? **logon**

```
*** It is now 2009/09/01 07:35:04 ***
 (Dialog time 2009/09/01 06:35:04)

Preferences:
1.  Default save option: [HTML]
2.  Graphic Images.
      Maximum width in pixels : [300]
      Maximum height in pixels: [300]
3.  Hold output position (don't scroll to the output buffer end): [Yes]
4.  Command separators (add HR after every command): [No]
5.  Type separators (add HR after every record): [Yes]
6.  Linking Pane: [Right]
7.  Status location.
      Below Type ahead buffer : [Yes]
      In Browser status line: [No]
8.  Show Estimated Cost Summary: [Yes]
9. Highlight Search Terms: [No]
10. Display Detailed Results by Search Term: [Yes]
11. Show Results by File (multifile search): [Yes]
12. Display Postings: [No]
14. Expand Items: 10
15. Hold Expand output position (don't scroll to the output buffer
end): [Yes]
16. KWIC Window: 30
17. Output Cost Notification: [No]
18. Prompt for Subaccount at Logon: [No]
19. Hide History Tab: [No]
20. Show Preferences at Login: [Yes]
21. Show hyphen(s) in display set command : [Yes]
```

Please enter a command or be logged off in 5 minutes

? **b 155 biosci medicine 399**

```
       01sep09 05:56:04 User276629 Session D275.1
            $0.00     0.253 DialUnits File415
     $0.00  Estimated cost File415
     $2.93  INTERNET
     $2.93  Estimated cost this search
     $2.93  Estimated total session cost   0.253 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1950-2009/Aug 28
         (c) format only 2009 Dialog
  File   5:Biosis Previews(R) 1926-2009/Aug W5
         (c) 2009 The Thomson Corporation
  File  24:CSA Life Sciences Abstracts 1966-2009/Sep
         (c) 2009 CSA.
  File  28:Oceanic Abstracts 1966-2009/Sep
         (c) 2009 CSA.
```

```
  File  34:SciSearch(R) Cited Ref Sci 1990-2009/Aug W4
        (c) 2009 The Thomson Corp
  File  35:Dissertation Abs Online 1861-2009/Jul
        (c) 2009 ProQuest Info&Learning
  File  40:Enviroline(R) 1975-2008/May
        (c) 2008 Congressional Information Service
*File  40: This file is closed and will no longer update. For
similar data, please search File 76-Environmental Sciences.
  File  41:Pollution Abstracts 1966-2009/Sep
        (c) 2009 CSA.
  File  44:Aquatic Science & Fisheries Abstracts 1966-2009/Sep
        (c) 2009 CSA.
  File  45:EMCare 2009/Aug W4
        (c) 2009 Elsevier B.V.
  File  50:CAB Abstracts 1972-2009/Aug W4
        (c) 2009 CAB International
  File  65:Inside Conferences 1993-2009/Aug 28
        (c) 2009 BLDSC all rts. reserv.
  File  71:ELSEVIER BIOBASE 1994-2009/Aug W5
        (c) 2009 Elsevier B.V.
*File  71: The file has been reloaded. Accession numbers
have changed.
  File  72:EMBASE 1993-2009/Aug 27
        (c) 2009 Elsevier B.V.
*File  72: EMBASE Classic (File 772) now open to all Dialog customers.
See HELP NEWS 772 for information.
  File  73:EMBASE 1974-2009/Aug 27
        (c) 2009 Elsevier B.V.
*File  73: EMBASE Classic available to all Dialog customers.
See HELP NEWS 772 for information.
  File  76:Environmental Sciences 1966-2009/Sep
        (c) 2009 CSA.
  File  91:MANTIS(TM) 1880-2009/Aug
        2001 (c) Action Potential
  File  98:General Sci Abs 1984-2009/Sep
        (c) 2009 The HW Wilson Co.
  File 110:WasteInfo 1974-2002/Jul
        (c)  2002 AEA Techn Env.
*File 110: This file is closed (no updates)
  File 135:NewsRx Weekly Reports 1995-2009/Aug W3
        (c) 2009 NewsRx
  File 136:BioEngineering Abstracts 1966-2007/Jan
        (c) 2007 CSA.
*File 136: This file is closed.
  File 143:Biol. & Agric. Index 1983-2009/Aug
        (c) 2009 The HW Wilson Co
  File 144:Pascal 1973-2009/Aug W5
        (c) 2009 INIST/CNRS
  File 154:MEDLINE(R) 1990-2009/Aug 28
        (c) format only 2009 Dialog
  File 164:Allied & Complementary Medicine 1984-2009/Aug
        (c) 2009 BLHCIS
  File 172:EMBASE Alert 2009/Aug 28
        (c) 2009 Elsevier B.V.
  File 185:Zoological Record Online(R) 1864-2009/Aug
        (c) 2009 The Thomson Corp.
  File 357:Derwent Biotech Res. _1982-2009/Jul W3
```

```
        (c) 2009 Thomson Reuters
  File 369:New Scientist 1994-2009/Aug W4
        (c) 2009 Reed Business Information Ltd.
  File 370:Science 1996-1999/Jul W3
        (c) 1999 AAAS
*File 370: This file is closed (no updates). Use File 47 for more
current
information.
  File 391:Beilstein Database - Reactions 2008/Q2
        (c) 2008 Beilstein GmbH
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
        (c) 2006 The Thomson Corp
  File 457:The Lancet 1992-2009/Aug W4
        (c) 2009 Elsevier Limited.All rights res
  File 467:ExtraMED(tm) 2000/Dec
        (c) 2001 Informania Ltd.
  File 138:Physical Education Index 1990-2009/Sep
        (c) 2009 CSA.
  File 149:TGG Health&Wellness DB(SM) 1976-2009/Aug W1
        (c) 2009 Gale/Cengage
  File 156:ToxFile 1965-2009/Aug W4
        (c) format only 2009 Dialog
  File 159:Cancerlit 1975-2002/Oct
        (c) format only 2002 Dialog
  File 162:Global Health 1983-2009/Aug W4
        (c) 2009 CAB International
  File 266:FEDRIP 2009/Jun
       Comp & dist by NTIS, Intl Copyright All Rights Res
  File 399:CA SEARCH(R) 1967-2009/UD=15110
        (c) 2009 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.
  File 444:New England Journal of Med. 1985-2009/Aug W4
        (c) 2009 Mass. Med. Soc.

      Set   Items   Description
      ---   -----   -----------
```

? **s (hemoglobin or haemoglobin)(n70)((red blood cell) or (red blood cells) or (RBC) or (RBCs))**

```
          656037  HEMOGLOBIN
          161088  HAEMOGLOBIN
           51992  RED BLOOD CELL
           30725  RED BLOOD CELLS
          107703  RBC
           44011  RBCS
      S1   20344  (HEMOGLOBIN OR HAEMOGLOBIN)(N70)((RED BLOOD CELL) OR
(RED
                  BLOOD CELLS) OR (RBC) OR (RBCS))
```

? **s s1(n60)(lysis or lyse)**

```
           20344  S1
          289265  LYSIS
           40987  LYSE
```

```
S2      357  S1(N60)(LYSIS OR LYSE)
```

? **s s2(n70)(freeze or frozen or (-80))**

```
          357  S2
       257152  FREEZE
       445425  FROZEN
            0  -80
S3          0  S2(N70)(FREEZE OR FROZEN OR (-80))
```

? **s s2 and (FREEZE OR FROZEN OR (-80))**

```
          357  S2
       257152  FREEZE
       445425  FROZEN
            0  -80
S4          1  S2 AND (FREEZE OR FROZEN OR (-80))
```

? **t s4/medium/1**

4/3/1 (Item 1 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

03048391 **Supplier Number:** 154512998 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Comparison of erythrocyte osmotic fragility among amphibians, reptiles, birds and mammals.

Aldrich, Kevin J.; Saunders, David K.; Sievert, Lynnette M.; Sievert, Greg
Transactions of the Kansas Academy of Science , 109 , 3-4 , 149(10)
Fall ,
2006
Publication Format: Magazine/Journal
ISSN: 0022-8443
Language: English
Record Type: Fulltext **Target Audience:** Academic
Word Count: 4273 **Line Count:** 00404

Descriptors: Erythrocyte disorders--Research; Amphibians--Physiological aspects; Amphibians--Environmental aspects; Amphibians--Research; Reptiles-- Physiological aspects; Reptiles--Environmental aspects; Reptiles--Research
Geographic Codes/Names: 1U4KS Kansas
Event Codes/Names: 310 Science & research

? **s ((red blood cell) or (red blood cells) or (RBC) or (RBCs))(n70)(lyse or lysis)(n70)(freeze or frozen or (-80))**

```
       51992  RED BLOOD CELL
```

```
         30725  RED BLOOD CELLS
        107703  RBC
         44011  RBCS
         40987  LYSE
        289265  LYSIS
        257152  FREEZE
        445425  FROZEN
             0  -80
S5          17  ((RED BLOOD CELL) OR (RED BLOOD CELLS) OR (RBC) OR
                (RBCS))(N70)(LYSE OR LYSIS)(N70)(FREEZE OR FROZEN OR
                (-80))
```

? **s ((red blood cell) or (red blood cells) or (RBC) or (RBCs))(n70)(lyse or lysis or rupture or break)(n70)(freeze or frozen or (-80))**

```
         51992  RED BLOOD CELL
         30725  RED BLOOD CELLS
        107703  RBC
         44011  RBCS
         40987  LYSE
        289265  LYSIS
        562862  RUPTURE
        328305  BREAK
        257152  FREEZE
        445425  FROZEN
             0  -80
S6          46  ((RED BLOOD CELL) OR (RED BLOOD CELLS) OR (RBC) OR
                (RBCS))(N70)(LYSE OR LYSIS OR RUPTURE OR
                BREAK)(N70)(FREEZE OR FROZEN OR (-80))
```

? **rd**

```
>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
S7          17  RD  (unique items)
```

? **s s7 and (hemoglobin or haemoglobin)**

```
            17  S7
        656037  HEMOGLOBIN
        161088  HAEMOGLOBIN
S8           1  S7 AND (HEMOGLOBIN OR HAEMOGLOBIN)
```

? **t s8/medium/1**

Dialog eLink: USPTO Full Text Retrieval Options

8/3/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

09291596 **PMID:** 2799892
Paroxysmal nocturnal hemoglobinuria and the transfusion of washed red cells. A

myth revisited.

Brecher M E; Taswell H F
Blood Bank and Transfusion Services, Mayo Clinic, Rochester, Minnesota.
Transfusion (UNITED STATES) Oct 1989 , 29 (8) p681-5 , **ISSN:** 0041-1132--Print
Journal Code: 0417360
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

? **s s7 not s8**

```
            17  S7
             1  S8
S9          16  S7 NOT S8
```

? **t s9/medium/all**

Dialog eLink: USPTO Full Text Retrieval Options
9/3/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

17782315 **PMID:** 17381616
Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice.

Johansson Par I; Stensballe Jakob; Rosenberg Iben; Hilslov Tanja L; Jorgensen Lisbeth; Secher Niels H
Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. p.johansson@post.tele.dk
Transfusion (United States) Apr 2007 , 47 (4) p593-8 , **ISSN:** 0041-1132--Print
Journal Code: 0417360
Publishing Model Print
Document type: Clinical Trial; Comparative Study; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
9/3/2 (Item 2 from file: 155)

DIALOG(R)File 155: MEDLINE(R)

16921294 **PMID:** 16371045
Delayed and acute hemolytic transfusion reactions resulting from red cell antibodies and red cell-reactive HLA antibodies.

Takeuchi Chikako; Ohto Hitoshi; Miura Saori; Yasuda Hiroyasu; Ono Satoshi; Ogata Takashi
Division of Blood Transfusion and Transplantation Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan.
Transfusion (United States) Dec 2005 , 45 (12) p1925-9 , **ISSN:** 0041-1132--Print
Journal Code: 0417360
Publishing Model Print
Document type: Case Reports; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

9/3/3 (Item 3 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

13516934 **PMID:** 10429773
[Cost analysis of autologous transfusion methods--a study of 5,017 patients]

Kostenanalyse autologer Transfusionsverfahren--eine Untersuchung bei 5017 Patienten.
Singbartl G; Schleinzer W
ENDO-Klinik Hamburg.
Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie - AINS (GERMANY) Jun 1999 , 34 (6) p350-8 , **ISSN:** 0939-2661--Print **Journal Code:** 9109478
Publishing Model Print
Document type: Clinical Trial; English Abstract; Journal Article
Languages: GERMAN
Main Citation Owner: NLM
Record type: MEDLINE; Completed

9/3/4 (Item 4 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

07650432 **PMID:** 6519067
Filipin as a cholesterol probe. II. Filipin-cholesterol interaction in red blood cell membranes.

Behnke O; Tranum-Jensen J; van Deurs B
European journal of cell biology (GERMANY, WEST) Nov 1984 , 35 (2) p200-15 , **ISSN:** 0171-9335--Print **Journal Code:** 7906240
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

9/3/5 (Item 5 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

05314798 **PMID:** 954179
Effect of different lysing and washing methods on free amino acid concentrations of sheep whole blood and erythrocytes.

Wolfrom G W; Asplund J M
Clinical biochemistry (CANADA) Aug 1976 , 9 (4) p180-3 , **ISSN:** 0009-9120--Print **Journal Code:** 0133660
Publishing Model Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

9/3/6 (Item 1 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)

0019597965 **Biosis No.:** 200700257706
Random healthy donor sera show varying effectiveness in hemolyzing ABO incompatible red blood cells.

Author: Dumont Larry J (Reprint); AuBuchon James P; Herschel Louise; Roger Jill; White Thayer; Stassinopoulos Adonis
Author Address: Dartmouth Hitchcock Med Ctr, Lebanon, NH 03766 USA**USA
Journal: Blood 108 (11, Part 1): p 286A NOV 16 2006 2006
Conference/Meeting: 48th Annual Meeting of the American-Society-of-Hematology Orlando, FL, USA December 09 -12, 2006; 20061209
Sponsor: Amer Soc Hematol
ISSN: 0006-4971
Document Type: Meeting; Meeting Poster
Record Type: Abstract
Language: English

9/3/7 (Item 2 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)

18626588 **Biosis No.:** 200510321088
Glycerol permeability and aquaporins from a freeze-tolerant amphibian that accumulates glycerol

Author: Goldstein David L (Reprint); Frisbie James; Krane Carissa
Author Address: Wright State Univ, Dayton, OH 45435 USA**USA
Journal: FASEB Journal 19 (5, Suppl. S, Part 2): p A1585 MAR 7 2005 2005
Conference/Meeting: Experimental Biology 2005 Meeting/35th International Congress of Physiological Sciences San Diego, CA, USA March 31 -April 06, 2005; 20050331
Sponsor: Amer Assoc Anatomists
Amer Assoc Immunologists
Amer Physiol Soc
Amer Soc Biochem & Mol Biol
Amer Soc Investigat Pathol
Amer Soc Nutr Sci
Amer Soc Pharmacol & Expt Therapeut
Int Union Physiol Sci
ISSN: 0892-6638
Document Type: Meeting; Meeting Abstract
Record Type: Abstract
Language: English

9/3/8 (Item 3 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)

16668160 **Biosis No.:** 200200261671
Ex vivo expansion of CB cells without CD34 selection using co-culture on MSC

Author: McNiece Ian K (Reprint); Harrington Jenny A (Reprint); James Rohaizah I (Reprint); Shpall Elizabeth J (Reprint); Mackay Alistair; Smith Alan
Author Address: Experimental Hematology, University of Colorado Health Sciences Center, Denver, CO, USA**USA
Journal: Blood 98 (11 Part 1): p 851a-852a November 16, 2001 2001
Medium: print
Conference/Meeting: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001; 20011207
Sponsor: American Society of Hematology
ISSN: 0006-4971
Document Type: Meeting; Meeting Abstract
Record Type: Abstract
Language: English

9/3/9 (Item 4 from file: 5)
DIALOG(R)File 5: Biosis Previews(R)

09557459 **Biosis No.:** 198987005350
DISCREPANCIES IN REVERSE ABO TYPING DUE TO PROZONE HOW SAFE IS THE IMMEDIATE-SPIN CROSSMATCH?

Author: JUDD W J (Reprint); STEINER E A; O'DONNELL D B; OBERMAN H A
Author Address: DEP PATHOL, UNIV MICH HOSP UH-2G332110054, 1500 E MEDICAL CENTER DR, ANN ARBOR, MICH 48109, USA**USA
Journal: Transfusion (Bethesda) 28 (4): p 334-338 1988
ISSN: 0041-1132
Document Type: Article
Record Type: Abstract
Language: ENGLISH

9/3/10 (Item 1 from file: 24)
DIALOG(R)File 24: CSA Life Sciences Abstracts

0003640518 IP Accession No: 6569463
IMMUNOHEMATOLOGY: Delayed and acute hemolytic transfusion reactions resulting from red cell antibodies and red cell-reactive HLA antibodies

Takeuchi, Chikako; Ohto, Hitoshi; Miura, Saori; Yasuda, Hiroyasu; Ono, Satoshi; Ogata, Takashi Division of Blood Transfusion and Transplantation Immunology, Fukushima Medical University School of Medicine, Fukushima, Japan, [mailto:hit-ohto@fmu.ac.jp]
Transfusion , v 45 , n 12 , p 1925-1929 , December 2005
Publication Date: 2005
Publisher: Blackwell Publishing Ltd., 9600 Garsington Road Oxford OX4 2DQ UK, [URL:http://www.blackwellpublishing.com]

Document Type: Journal Article
Record Type: Abstract
Language: English
Summary Language: English
ISSN: 0041-1132
Electronic Issn: 15372995
File Segment: Immunology Abstracts

0003326796 IP Accession No: 8219853
Novel nanoporous membranes from regenerated bacterial cellulose

Phisalaphong, Muenduen; Suwanmajo, Thapanar; Sangtherapitikul, Preecha Department of Chemical Engineering, Chulalongkorn University, Bangkok 10330, Thailand, [mailto:muenduen.p@chula.ac.th]
Journal of Applied Polymer Science , v 107 , n 1 , p 292-299 , January 2008
Publication Date: 2008
Publisher: John Wiley & Sons, Baffins Lane Chichester W. Sussex PO19 1UD UK, [mailto:customer@wiley.co.uk], [URL:http://www.wiley.com/]

Document Type: Journal Article
Record Type: Abstract
Language: English
Summary Language: English
ISSN: 0021-8995
Electronic Issn: 1097-4628
File Segment: Bacteriology Abstracts (Microbiology B)

9/3/12 (Item 1 from file: 34)
DIALOG(R)File 34: SciSearch(R) Cited Ref Sci

07842356 **Genuine Article#:** 214PH **No. References:** 26
Cost analysis of autologous transfusion methods - A study on 5,017 patients

Author: Singbartl G (REPRINT) ; Schleinzer W
Corporate Source: AIT ENDO KLIN HAMBURG,HOLSTENSTR 2/D-22767 HAMBURG//GERMANY/ (REPRINT); NEUE PREGAMON KRANKENHAUS MANAGEMENT GMBH,/HEILBRONN//GERMANY/; SCHWIEZER PARAPLEGIKER ZENTRUM,/NOTTWIL//GERMANY/
Journal: ANASTHESIOLOGIE INTENSIVMEDIZIN NOTFALLMEDIZIN SCHMERZTHERAPIE , 1999 , V 34 , N6 (JUN) , P 350-358
ISSN: 0939-2661 **Publication date:** 19990600
Publisher: GEORG THIEME VERLAG , P O BOX 30 11 20, D-70451 STUTTGART, GERMANY
Language: German **Document Type:** ARTICLE (ABSTRACT AVAILABLE)

9/3/13 (Item 1 from file: 45)
DIALOG(R)File 45: EMCare

0003609607 **EMCARE No:** 29329593
Cost analysis of autologous transfusion methods - A study on 5,017 patients

Kostenanalyse autologer transfusionsverfahren - Eine untersuchung bei 5017 patienten
Singbartl C.; Schleinzer W.
CORRESP. AUTHOR/AFFIL: Singbartl G.: AIT - ENDO-Klinik Hamburg, Holstenstrasse 2, D-22767 Hamburg, Germany

Anasthesiologie Intensivmedizin Notfallmedizin Schmerztherapie (Anasthesiol. Intensivmed. Notf.med. Schmerzther.) (Germany) June 1, 1999 , 34/6 (350-358)
PUBLISHER: Georg Thieme Verlag
CODEN: AISTE **ISSN:** 0939-2661
DOI: 10.1055/s-1999-8741
Item Identifier (DOI): 10.1055/s-1999-8741
DOCUMENT TYPE: Journal ; Article **RECORD TYPE:** Abstract
LANGUAGE: German **SUMMARY LANGUAGE:** English; German
NUMBER OF REFERENCES: 26

9/3/14 (Item 1 from file: 135)
DIALOG(R)File 135: NewsRx Weekly Reports

0000512556 (USE FORMAT 7 OR 9 FOR FULLTEXT)

Reports from University of Copenhagen, Department of Clinical Immunology describe recent advances in abdominal aortic aneurysm therapy
Blood Weekly, May 10, 2007, p.54

DOCUMENT TYPE: Expanded Reporting
LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 392

9/3/15 (Item 1 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

03178181 **Supplier Number:** 160737822 (USE FORMAT 7 OR 9 FOR FULL TEXT
)
Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice.(Author abstract)

Johansson, Par I.; Stensballe, Jakob; Rosenberg, Iben; Hilslov, Tanja L.; Jorgensen, Lisbeth; Secher, Niels H.
Transfusion , 47 , 4 , 593(6)
April ,
2007
Document Type: Author abstract **Publication Format:** Magazine/Journal
ISSN: 0041-1132
Language: English
Record Type: Abstract **Target Audience:** Academic

Descriptors: Aneurysms

9/3/16 (Item 1 from file: 159)
DIALOG(R)File 159: Cancerlit

01052009 PMID: 75603457
UPTAKE OF PROTEINS BY RED BLOOD CELLS.

Rechsteiner
Dept. Biology, Univ. Utah, Salt Lake City, Utah 84112
Exp Cell Res
1975 ,
93 (2) p487-492 , ISSN 0014-4827
Document Type: JOURNAL ARTICLE
Languages: ENGLISH
Main Citation Owner: NOTNLM
Record type: Completed

? **t s9/full/5**

9/9/5 (Item 5 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

05314798 **PMID:** 954179
Effect of different lysing and washing methods on free amino acid concentrations of sheep whole blood and erythrocytes.

Wolfrom G W; Asplund J M
Clinical biochemistry (CANADA) Aug 1976 , 9 (4) p180-3 , **ISSN:** 0009-9120--Print **Journal Code:** 0133660
Publishing Model Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
1. A study was conducted to determine the effect of different washing and lysing methods on the free amino acid concentrations of sheep erythryocytes (RBC) and whole blood. Methods of lysis included laking, freeze-thawing or sonication. RBC were washed with isotonic solutions of either saline or sucrose. 2. Washing the RBC with isotonic sucrose resulted in significantly greater concentrations for ten of the amino acids. Greater amino acid concentrations were realized when washed RBC were sonicated and when the RBC of whole blood were lysed by laking. 3. Suggestions are made for future application to whole blood and RBC amino acid determinations.
Descriptors: *Amino Acids--blood--BL; *Erythrocytes--analysis--AN ; Animals; Evaluation Studies as Topic; Hemolysis; Methods; Sheep
CAS Registry No.: 0 (Amino Acids)
Record Date Created: 19761101

Record Date Completed: 19761101

? **s (blood)(n70)(freeze or frozen or (freeze-thaw) or (-80))**

```
Processing
Processing
Processing
Processing
Processing
Processed  20 of  42 files ...
Processing
Completed processing all files
        15437834  BLOOD
          257152  FREEZE
          445425  FROZEN
             954  FREEZE-THAW
               0  -80
     S10   47705  (BLOOD)(N70)(FREEZE OR FROZEN OR (FREEZE-THAW) OR (-
80))
```

? **s s10(n100)(hemoglobin or haemoglobin or Hb)**

```
           47705  S10
          656037  HEMOGLOBIN
          161088  HAEMOGLOBIN
          233636  HB
     S11    2010  S10(N100)(HEMOGLOBIN OR HAEMOGLOBIN OR HB)
```

? **s s10(n100)((hemoglobin or haemoglobin or Hb)(n50)(purif?))**

```
Processing
           47705  S10
          656037  HEMOGLOBIN
          161088  HAEMOGLOBIN
          233636  HB
         4028171  PURIF?
     S12      51  S10(N100)((HEMOGLOBIN OR HAEMOGLOBIN OR
HB)(N50)(PURIF?))
```

? **rd**

```
>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
     S13      19  RD  (unique items)
```

? **s s13/medium/all**

```
>>>Possible typing error near /
```

? **t s13/medium/all**

Dialog eLink: USPTO Full Text Retrieval Options
13/3/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

17948132 **PMID:** 17393480
Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique".

Terada Nobuo; Ohno Nobuhiko; Saitoh Sei; Fujii Yasuhisa; Ohguro Hiroshi; Ohno Shinichi
Department of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Chuo-city, Yamanashi 409-3898, Japan. nobuot@yamanashi.ac.jp
Microscopy research and technique (United States) Jul 2007 , 70 (7) p634-9 , **ISSN:** 1059-910X--Print **Journal Code:** 9203012
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/2 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

12318632 **PMID:** 9054405
The globin-based free radical of ferryl hemoglobin is detected in normal human blood.

Svistunenko D A; Patel R P; Voloshchenko S V; Wilson M T
Department of Biological and Chemical Sciences, Central Campus, University of Essex, Colchester, Essex CO4 3SQ, United Kingdom.
Journal of biological chemistry (UNITED STATES) Mar 14 1997 , 272 (11) p7114-21 , **ISSN:** 0021-9258--Print **Journal Code:** 2985121R
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/3 (Item 3 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

11308907 **PMID:** 7994369
Stabilized hemoglobin vesicles.

Tsuchida E
Department of Polymer Chemistry, Waseda University, Tokyo, Japan.
Artificial cells, blood substitutes, and immobilization biotechnology (UNITED STATES) 1994 , 22 (3) p467-77 , **ISSN:** 1073-1199--Print **Journal Code:** 9431307
Publishing Model Print
Document type: In Vitro; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/4 (Item 4 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10533593 **PMID:** 1457926
Characteristics of artificial red cells. Hemoglobin encapsulated in poly-lipid vesicles.

Satoh T; Kobayashi K; Sekiguchi S; Tsuchida E
Tsukuba Research Laboratories, NOF Corporation, Japan.
ASAIO journal (American Society for Artificial Internal Organs - 1992) (UNITED STATES) Jul-Sep 1992 , 38 (3) pM580-4 , **ISSN:** 1058-2916--Print **Journal Code:** 9204109
Publishing Model Print
Document type: In Vitro; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/5 (Item 5 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10049338 **PMID:** 1918801
Preparation of unaltered hemoglobin from human placentas for possible use in blood substitutes.

Fasan G; Grandgeorge M; Vigneron C; Dellacherie E
CNRS URA 494, ENSIC, Nancy, France.
Journal of biochemical and biophysical methods (NETHERLANDS) Jul-Aug 1991 , 23 (1) p53-66 , **ISSN:** 0165-022X--Print **Journal Code:** 7907378
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

13/3/6 (Item 6 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

09774516 **PMID:** 2289306
Polymerase chain reaction: amplification of DNA from fixed tissue.

Crisan D; Cadoff E M; Mattson J C; Hartle K A
Department of Pathology, University of Pittsburgh, PA 15213-2582.
Clinical biochemistry (CANADA) Dec 1990 , 23 (6) p489-95 , **ISSN:** 0009-9120--Print **Journal Code:** 0133660
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

13/3/7 (Item 7 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

05307246 **PMID:** 951729
Preparation of antihemophilic factor from indated plasma.

Wickerhauser M

Transfusion (UNITED STATES) Jul-Aug 1976 , 16 (4) p345-50 , **ISSN:** 0041-1132--Print **Journal Code:** 0417360
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/8 (Item 8 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

04293564 **PMID:** 5005879
Recent advances in the field of red cell structure.

Baker R F
Pathobiology annual (UNITED STATES) 1971 , 1 p95-137 , **ISSN:** 0362-3025--Print **Journal Code:** 1305471
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Dialog eLink: USPTO Full Text Retrieval Options
13/3/9 (Item 1 from file: 50)
DIALOG(R)File 50: CAB Abstracts

0008083726 **CAB Accession Number:** 20013088268
Gemobin - a new-generation natural biologically active food supplement.

Chernyaev, S. I.; Lyublinskii, S. L.; Lyublinskaya, I. N.; Markov, M. V.
Dep. Sel'skogo Khozyaistva I Prodovol'stviya, Kaluga obl., Russia.
Pishchevaya Promyshlennost' (6): p.50-52
Publication Year: 2000
ISSN: 0235-2486
Publisher: OOO "Pishchepromizdat" Moscow , Russia
Language: Russian **Record Type:** Abstract
Document Type: Journal article

13/3/10 (Item 1 from file: 71)
DIALOG(R)File 71: ELSEVIER BIOBASE

0007196715 **Supplier Number:** 2007196786
Raman microscopy of freeze-derived mouse eyeball-slice in conjunction with "in vivo cryotechnique"
Terada N.; Ohno N.; Saitoh S.; Fujii Y.; Ohguro H.; Ohno S.
Author Email: nobuot@yamanashi.ac.jp
Corresp. Author/Affil: Terada N., Department of Anatomy, Interdisciplinary Graduate School of, Medicine and Engineering, University of Yamanashi, 1110 Shimokato, Chuo-city, Yamanashi 409-3898 , Japan
Corresp. Author Email: nobuot@yamanashi.ac.jp
Journal : Microscopy Research and Technique (Microsc. Res. Tech.) , v70, n7, (634-639) , 2007 , United States
Publication Date: July 1, 2007 (20070701)
Coden: MRTEE
ISSN: 1059-910X **eISSN:** 1097-0029
Record Type: Abstract; New
Document Type: Article
Languages: English **Summary Languages:** English
No. of References: 20

Descriptors:
Freeze-drying; In vivo cryotechnique; Mapping; Raman microscopy; Raman spectrum

Classification Code and Description:
89 (CELL AND DEVELOPMENTAL BIOLOGY)
89.13 (METHODOLOGY)
89.13.1 (Techniques)
89.13.1.3 (Microscopy)

Record History: New; Created: July 20, 2007 (20070720) ; Delivered: June 22, 2008 (20080622)
Dialog Update Date: 20081211; 08:07:19 EST

13/3/11 (Item 1 from file: 73)
DIALOG(R)File 73: EMBASE

0071381872 **EMBASE No:** 1979114101
Analysis of iron content in individual human red blood cells by electron

microprobe and scanning electron microscope

Davis D.
Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States
Corresp. Author/Affil: : Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

Micron (MICRON) (United Kingdom) December 1, 1978 , 9/4 (175-190)
CODEN: MICNB **ISSN:** 0968-4328
Document Type: Journal **Record Type:** Abstract
Language: English

13/3/12 (Item 2 from file: 73)
DIALOG(R)File 73: EMBASE

0070101518 **EMBASE No:** 1974101617
Iron ATP, a by product of acid extraction of whole blood or red blood cells

Meyers N.L.; Brewer G.J.; Oelshlegel Jr F.J.
Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States
Corresp. Author/Affil: : Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States

Biochimica et Biophysica Acta (BIOCHIM. BIOPHYS. ACTA) December 1, 1973 , 320/2 (397-405)
CODEN: BBACA **ISSN:** 0006-3002
Document Type: Journal **;** Article **Record Type:** Abstract
Language: English

13/3/13 (Item 1 from file: 135)
DIALOG(R)File 135: NewsRx Weekly Reports

0000571468 (USE FORMAT 7 OR 9 FOR FULLTEXT)

Studies in the area of microscopy reported from University of Yamanashi
Life Science Weekly, July 24, 2007, p.2754

DOCUMENT TYPE: Expanded Reporting
LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 427

13/3/14 (Item 2 from file: 135)
DIALOG(R)File 135: NewsRx Weekly Reports

0000000087 (USE FORMAT 7 OR 9 FOR FULLTEXT)

Hemolink Phase II Trials to Begin in 1996
AIDS Weekly, December 25, 1995, p.11-12

DOCUMENT TYPE: Editor's Choice
LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 763

13/3/15 (Item 1 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

01812276 **Supplier Number:** 53480462 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Blood relations.(Hemosol Inc's packaging for blood substitute products)

Canadian Packaging , 51 , 11 , 34(1)
Nov ,
1998
Publication Format: Magazine/Journal
ISSN: 0008-4654
Language: English
Record Type: Fulltext **Target Audience:** Trade
Word Count: 1076 **Line Count:** 00094

Special Features: illustration; 1
Company Names: Hemosol Inc.--Products
Descriptors: Blood substitutes--Packaging; Blood products--Packaging; Packaging industry --Products
Geographic Codes/Names: 1USA United States
SIC Codes: 2836 Biological products exc. diagnostic; 2670 Misc. Converted Paper

Products
Event Codes/Names: 460 Use of materials & supplies
Product/Industry Names: 2833440 (Synthetic Blood); 2649910 (Sterilized Medical Packaging)
File Segment: TI File 148

13/3/16 (Item 2 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

01641618 **Supplier Number:** 18748015 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Blood substitute offers advantages. (experimental Hemolink, a red blood cell substitute from Hemosol Inc, does not possess the disadvantages of donated blood)(Brief Article)

USA Today (Magazine) , v124 , n2609 , p13(1)
Feb ,
1996
Document Type: Brief Article **Publication Format:** Magazine/Journal
ISSN: 0161-7389
Language: English
Record Type: Fulltext **Target Audience:** Consumer
Word Count: 459 **Line Count:** 00041

Special Features: illustration; photograph
Company Names: Hemosol Inc.--Product development
Descriptors: Blood substitutes--Innovations
File Segment: MI File 47

13/3/17 (Item 3 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

01193508 **Supplier Number:** 08093457 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Synthesis of functional human hemoglobin in transgenic mice.

Behringer, Richard R.; Ryan, Thomas M.; Reilly, Michael P.; Asakura, Toshio ; Palmiter, Richard D.; Brinster, Ralph L.; Townes, Tim M.
Science , v245 , n4921 , p971(3)
Sept 1 ,
1989
Publication Format: Magazine/Journal
ISSN: 0036-8075

Language: English
Record Type: Fulltext **Target Audience:** Academic
Word Count: 2144 **Line Count:** 00213

Special Features: illustration; chart; graph
Descriptors: Mice as laboratory animals--Research; Gene expression--Research; Hemoglobinopathy--Models; Genetic transformation--Research; Hemoglobin-- Research
File Segment: MI File 47

13/3/18 (Item 1 from file: 162)
DIALOG(R)File 162: Global Health

0004754137 **CAB Accession Number:** 20002007317
KEMRI Hep-cell II hepatitis B surface antigen screening kit.

Okoth, F. A.; Kaiguri, P. M.; Mathenge, E.; Tuei, J.; Muchiri, S.; Owino, N.; Kamau, G.; Kulundu, J.; Njuguna, A.; Tukei, P. M.; Yano, M.; Naruse, T.
Virus Research Centre, Kenya Medical Research Institute, P.O. Box 54628, Nairobi, Kenya.
East African Medical Journal vol. 76 (9): p.530-532
Publication Year: 1999
ISSN: 0012-835X
Language: English **Record Type:** Abstract
Document Type: Journal article

13/3/19 (Item 1 from file: 444)
DIALOG(R)File 444: New England Journal of Med.

00103092

Elevated Fetal Hemoglobin Levels in Sudden Infant Death Syndrome (Original Article)

Giulian, Gary G., B.A.; Gilbert, Enid F.; Moss, Richard L., Ph.D.
The New England Journal of Medicine
April 30 , 1987 ; 316 (18),pp 1122-1126

Line Count: 00337 **Word Count:** 04654

? **t s13/full/all**

Dialog eLink:
13/9/1 (Item 1 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

17948132 **PMID:** 17393480
Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique".

Terada Nobuo; Ohno Nobuhiko; Saitoh Sei; Fujii Yasuhisa; Ohguro Hiroshi; Ohno Shinichi
Department of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Chuo-city, Yamanashi 409-3898, Japan. nobuot@yamanashi.ac.jp
Microscopy research and technique (United States) Jul 2007 , 70 (7) p634-9 , **ISSN:** 1059-910X--Print **Journal Code:** 9203012
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying. Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy. Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively. Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for

examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue.
Descriptors: *Cryopreservation--methods--MT; *Eye--anatomy and histology--AH; *Eye --chemistry--CH; *Microscopy, Confocal--methods--MT; *Spectrum Analysis, Raman--methods--MT ; Animals; Cryoultramicrotomy--methods--MT; Freeze Drying; Hemoglobins --analysis--AN; Mice; Preservation, Biological; Rhodopsin--analysis--AN; Specimen Handling
CAS Registry No.: 0 (Hemoglobins); 9009-81-8 (Rhodopsin)
Record Date Created: 20070625
Record Date Completed: 20070731

13/9/2 (Item 2 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

12318632 **PMID:** 9054405
The globin-based free radical of ferryl hemoglobin is detected in normal human blood.

Svistunenko D A; Patel R P; Voloshchenko S V; Wilson M T
Department of Biological and Chemical Sciences, Central Campus, University of Essex, Colchester, Essex CO4 3SQ, United Kingdom.
Journal of biological chemistry (UNITED STATES) Mar 14 1997 , 272 (11) p7114-21 , **ISSN:** 0021-9258--Print **Journal Code:** 2985121R
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
Normal human venous blood was studied by electron paramagnetic resonance (EPR) spectroscopy at -196 degrees C. The EPR signal of free radicals in frozen blood is shown to have the same radiospectroscopic parameters and properties as the signal of the globin based free radical, .Hb(Fe(IV)=O), formed in the reaction of purified methemoglobin (metHb) with H2O2 and therefore has been assigned as such. The globin-based radicals and metHb exhibited significant variation (fluctuations) in different frozen samples taken from the same liquid blood sample. In any given sample a high concentration of free radicals was associated with a low concentration of metHb and vice versa, i.e. the fluctuations were always of opposite sense. No such fluctuations were observed in the concentration of two other paramagnetic components of blood, transferrin and ceruloplasmin. The time course of free radical formation and decay upon the addition of H2O2 to purified metHb was studied at three different molar ratios H2O2/metHb. This kinetic study together with the results of an annealing experiment allow us to propose a

mechanism for the formation and decay of the globin-based radical in blood. Within this mechanism, the source of H2O2 in blood is considered to be dismutation of O-2 radicals produced via autoxidation of Hb. We postulate that the dismutation is intensified on the phase separation surfaces during cooling and freezing of a blood sample. The fluctuations are explained within this hypothesis.
Descriptors: *Globins--chemistry--CH; *Hemoglobins--chemistry--CH ; Electron Spin Resonance Spectroscopy; Free Radicals--blood--BL; Humans; Iron--chemistry--CH
CAS Registry No.: 0 (Free Radicals); 0 (Hemoglobins); 7439-89-6 (Iron); 9004-22-2 (Globins)
Record Date Created: 19970417
Record Date Completed: 19970417

13/9/3 (Item 3 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

11308907 **PMID:** 7994369
Stabilized hemoglobin vesicles.

Tsuchida E
Department of Polymer Chemistry, Waseda University, Tokyo, Japan.
Artificial cells, blood substitutes, and immobilization biotechnology (UNITED STATES) 1994 , 22 (3) p467-77 , **ISSN:** 1073-1199--Print **Journal Code:** 9431307
Publishing Model Print
Document type: In Vitro; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
The Hb-vesicles which encapsulate the purified and concentrated Hb more than 40 g/dl with a uni- or bi-lamellar membrane are prepared by extruding the dispersion of mixed lipids through membrane filters (final pore size: 0.2 micron phi). They transport large amount of oxygen with satisfying rheological properties such as oncotic pressure and solution viscosity. Oxygen affinity of the Hb-vesicles is adjusted so as to exceed the ability of oxygen transport of human blood by coencapsulating allosteric effectors in the Hb-vesicles. The solution is sterilizable because of the diameter of Hb vesicles less than 0.2 micron phi. The Hb-vesicles are stabilized by using polyphospholipid or glycolipid as membrane components. No change in oxygen affinity and particle size was confirmed during long time storage at 4 degrees C. The stabilized Hb-vesicles can also be stored as frozen or dried state. The dried Hb-vesicles are regenerated by simply adding pure water. Simple in vitro test indicates that Hb-vesicles have the reduced inhibitory action of Hb to the EDRF-mediated vasorelaxation.
Tags: Female; Male

Descriptors: *Blood Substitutes--isolation and purification--IP; *Hemoglobins--isolation and purification--IP ; Acetylcholine--antagonists and inhibitors--AI; Acetylcholine--pharmacology --PD; Animals; Blood Substitutes--chemistry--CH; Blood Substitutes --pharmacology--PD; Drug Stability; Drug Storage; Hemoglobins--chemistry --CH; Hemoglobins--pharmacology--PD; Humans; Liposomes; Nitric Oxide --antagonists and inhibitors--AI; Nitric Oxide--pharmacology--PD; Particle Size; Rabbits; Solutions; Vasodilation--drug effects--DE; Vehicles
CAS Registry No.: 0 (Blood Substitutes); 0 (Hemoglobins); 0 (Liposomes); 0 (Solutions); 0 (Vehicles); 0 (hemoglobin, stroma free); 10102-43-9 (Nitric Oxide); 51-84-3 (Acetylcholine)
Record Date Created: 19950117
Record Date Completed: 19950117

13/9/4 (Item 4 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10533593 **PMID:** 1457926
Characteristics of artificial red cells. Hemoglobin encapsulated in poly-lipid vesicles.

Satoh T; Kobayashi K; Sekiguchi S; Tsuchida E
Tsukuba Research Laboratories, NOF Corporation, Japan.
ASAIO journal (American Society for Artificial Internal Organs - 1992) (UNITED STATES) Jul-Sep 1992 , 38 (3) pM580-4 , **ISSN:** 1058-2916--Print **Journal Code:** 9204109
Publishing Model Print
Document type: In Vitro; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS; Toxbib
Artificial red cells (ARC) were prepared by encapsulation of purified human Hb with polymerizable phospholipid, 1,2-bis (2,4-octadecadienoyl)-sn-glycero-3-phosphocholine (DODPC). The polymerized lipid bilayer of the ARC produced great physical stability that could not be achieved using a non-polymerizable lipid for encapsulation. ARC showed no change in particle size or distribution or leakage of Hb after repeated freeze thawing (stability test). ARC have also been studied with regard to biocompatibility. The authors' results showed low acute toxicity (> 8000 mg/kg) and adequate blood compatibility. The result of transfusion tests in dogs showed that ARC had sufficient oxygen transporting capabilities.
Tags: Male
Descriptors: *Blood Substitutes; *Hemoglobins ; Animals; Biocompatible Materials; Blood Substitutes--isolation and purification--IP; Blood Substitutes--toxicity--TO; Dogs;

Drug Stability; Erythrocyte Aggregation; Evaluation Studies as Topic; Exchange Transfusion, Whole Blood; Freezing; Humans; Liposomes; Materials Testing; Oxygen--blood --BL; Phosphatidylcholines; Rats; Rats, Sprague-Dawley
CAS Registry No.: 0 (Biocompatible Materials); 0 (Blood Substitutes); 0 (Hemoglobins); 0 (Liposomes); 0 (Phosphatidylcholines); 7782-44-7 (Oxygen)
Record Date Created: 19930111
Record Date Completed: 19930111

13/9/5 (Item 5 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

10049338 **PMID:** 1918801
Preparation of unaltered hemoglobin from human placentas for possible use in blood substitutes.

Fasan G; Grandgeorge M; Vigneron C; Dellacherie E
CNRS URA 494, ENSIC, Nancy, France.
Journal of biochemical and biophysical methods (NETHERLANDS) Jul-Aug 1991 , 23 (1) p53-66 , **ISSN:** 0165-022X--Print **Journal Code:** 7907378
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
Hemoglobin extracted from human placentas could be used as the basis of blood substitutes provided it could be prepared on a large scale with appropriate oxygen-binding properties. Unfortunately, the industrial conditions under which it is extracted, produce hemoglobin with high oxygen affinity and which is no longer influenced by the classical effectors. These characteristics were shown to be caused by a degradation of the alpha-chain brought about by an arginine carboxypeptidase present in the placental tissues and leading to the disappearance of the C-terminal arginine residue. This carboxypeptidase which is released from the tissues during the process of crushing the frozen placentas, degrades the protein during the chromatographic purification procedure. The addition of an inhibitor of this carboxypeptidase (for example, arginine) as soon as the placentas are thawed and during the chromatographic process, makes it possible to obtain placental hemoglobin with oxygen-binding properties quite similar to those of HbA prepared from peripheral venous blood.
Descriptors: *Blood Substitutes--chemistry--CH; *Hemoglobins--isolation and purification --IP; *Placenta--chemistry--CH ; Adult; Arginine--pharmacology--PD; Carboxypeptidase B; Carboxypeptidases --pharmacology--PD; Hemoglobin A--drug effects--DE; Hemoglobins--chemistry --CH; Humans; Oxygen--blood--BL; Plasma--

physiology--PH; Protein Binding
CAS Registry No.: 0 (Blood Substitutes); 0 (Hemoglobins); 74-79-3 (Arginine); 7782-44-7 (Oxygen); 9034-51-9 (Hemoglobin A)
Enzyme No.: EC 3.4.- (Carboxypeptidases); EC 3.4.17.2 (Carboxypeptidase B)
Record Date Created: 19911028
Record Date Completed: 19911028

13/9/6 (Item 6 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

09774516 **PMID:** 2289306
Polymerase chain reaction: amplification of DNA from fixed tissue.

Crisan D; Cadoff E M; Mattson J C; Hartle K A
Department of Pathology, University of Pittsburgh, PA 15213-2582.
Clinical biochemistry (CANADA) Dec 1990 , 23 (6) p489-95 , **ISSN:** 0009-9120--Print **Journal Code:** 0133660
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
The polymerase chain reaction (PCR) allows the analysis of DNA from biologic samples containing only nanogram quantities of DNA. We used DNA purified from fresh or frozen peripheral blood (PB) leukocytes and formalin, or B-5 fixed bone marrow aspirate clots (BM). A sequence of the beta-globin gene was amplified via the PCR then hybridized with allele specific oligonucleotide probes for hemoglobin A, S, and C. All DNA preparations, including formalin and B-5 fixed BMs, were successfully amplified; the hybridization of the amplified products resulted in patterns consistent with the hemoglobin phenotype for all patients. PCR can be used on DNA from many sources; retrospective studies using paraffin embedded fixed tissue are possible because extremely small amounts of DNA present in fixed tissue can be successfully amplified.
Tags: Female; Male
Descriptors: *Polymerase Chain Reaction--methods--MT ; Adult; Aged; Aged, 80 and over; Base Sequence; DNA--genetics--GE; DNA Probes; DNA, Single-Stranded--genetics--GE; Fixatives; Formaldehyde; Humans ; Middle Aged; Molecular Sequence Data; Nucleic Acid Hybridization; Specimen Handling--methods--MT
CAS Registry No.: 0 (DNA Probes); 0 (DNA, Single-Stranded); 0 (Fixatives); 50-00-0 (Formaldehyde); 9007-49-2 (DNA)
Record Date Created: 19910329

Record Date Completed: 19910329

Dialog eLink: USPTO Full Text Retrieval Options
13/9/7 (Item 7 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

05307246 **PMID:** 951729
Preparation of antihemophilic factor from indated plasma.

Wickerhauser M
Transfusion (UNITED STATES) Jul-Aug 1976 , 16 (4) p345-50 , **ISSN:** 0041-1132--Print **Journal Code:** 0417360
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
Four large-scale batches of Antihemophilic Factor (AHF, factor VIII) were prepared from plasma derived from 4 to 6-day-old blood applying a method developed for preparation of AHF from fresh frozen plasma. The AHF product was 6 to 9-fold concentrated over plasma with 7 to 10-fold purification and a recovery of 100 to 140 factor VIII units per liter of starting plasma. In terms of purity and yield, this is about half that of AHF obtained from fresh frozen plasma. The AHF concentrate was free of detectable thrombin and plasmin and the solubility of the dry product was comparable to that of the product derived from fresh plasma but the hemoglobin content was slightly increased. After further fractionation with polyethylene glycol (PEG 4000), a highly soluble AHF product 100-fold purified, and 30-fold concentrated, was obtained with 60% factor VIII recovery, which corresponds to a final yield of 60 to 85 factor VIII units per liter of starting plasma.
Descriptors: *Factor VIII--isolation and purification--IP; *Plasma ; Factor VIII--analysis--AN; Fractional Precipitation; Hemoglobins--analysis --AN; Humans; Polyethylene Glycols; Time Factors
CAS Registry No.: 0 (Hemoglobins); 0 (Polyethylene Glycols); 9001-27-8 (Factor VIII)
Record Date Created: 19761002
Record Date Completed: 19761002

Dialog eLink: USPTO Full Text Retrieval Options
13/9/8 (Item 8 from file: 155)
DIALOG(R)File 155: MEDLINE(R)

04293564 **PMID:** 5005879
Recent advances in the field of red cell structure.

Baker R F
Pathobiology annual (UNITED STATES) 1971 , 1 p95-137 , **ISSN:** 0362-3025--Print **Journal Code:** 1305471
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Subfile: INDEX MEDICUS
(130 Refs.)
Descriptors: *Erythrocytes--cytology--CY ; Adenosine Triphosphate--isolation and purification--IP; Amino Acids--blood --BL; Anemia, Sickle Cell--blood--BL; Anemia, Sickle Cell--pathology--PA; Animals; Blood; Blood Group Antigens; Cell Membrane--analysis--AN; Cytological Techniques; Erythrocytes--analysis--AN; Erythrocytes --immunology--IM; Freeze Etching; Glutaral; Guinea Pigs; Hemoglobin, Sickle --analysis--AN; Humans; Lipids--blood--BL; Magnetic Resonance Spectroscopy; Microscopy, Electron; Microscopy, Electron, Scanning; Microtubules; Proteins--analysis--AN
CAS Registry No.: 0 (Amino Acids); 0 (Blood Group Antigens); 0 (Hemoglobin, Sickle); 0 (Lipids); 0 (Proteins); 111-30-8 (Glutaral); 56-65-5 (Adenosine Triphosphate)
Record Date Created: 19740328
Record Date Completed: 19740328

13/9/9 (Item 1 from file: 50)
DIALOG(R)File 50: CAB Abstracts

0008083726 **CAB Accession Number:** 20013088268
Gemobin - a new-generation natural biologically active food supplement.

Chernyaev, S. I.; Lyublinskii, S. L.; Lyublinskaya, I. N.; Markov, M. V.
Dep. Sel'skogo Khozyaistva I Prodovol'stviya, Kaluga obl., Russia.
Pishchevaya Promyshlennost' (6): p.50-52
Publication Year: 2000
ISSN: 0235-2486
Publisher: OOO "Pishchepromizdat" Moscow , Russia
Language: Russian **Record Type:** Abstract
Document Type: Journal article
Gemobin [Haemobin] is a purified native freeze-dried haemoglobin from the blood of cattle, containing 0.2-0.3% iron (bivalent form). This preparation is produced on an industrial scale in Russia by the Mobitek company, in the form of tablets, sugared

'plums', and Supergematogen sticks with a coconut filling. It is designed to remedy iron deficiency, and a comparison is made between Russia and Western countries in approaches to treating iron deficiency.

Descriptors: deficiency; food supplements; haemoglobin; iron; mineral supplements; supplements; trace elements
Identifiers: hemoglobin; microelements
CAS Registry Numbers: 7439-89-6
Organism Descriptors: man
Geographic Names: Russia
Broader Terms: Homo; Hominidae; Primates; mammals; vertebrates; Chordata; animals; eukaryotes; Asia; Central Europe; Europe; Developed Countries
CABICodes: Nutrition related Disorders and Therapeutic Nutrition (VV130); Meat Produce (QQ030)

13/9/10 (Item 1 from file: 71)
DIALOG(R)File 71: ELSEVIER BIOBASE

0007196715 **Supplier Number:** 2007196786
Raman microscopy of freeze-derived mouse eyeball-slice in conjunction with "in vivo cryotechnique"
Terada N.; Ohno N.; Saitoh S.; Fujii Y.; Ohguro H.; Ohno S.
Author Email: nobuot@yamanashi.ac.jp
Corresp. Author/Affil: Terada N., Department of Anatomy, Interdisciplinary Graduate School of, Medicine and Engineering, University of Yamanashi, 1110 Shimokato, Chuo-city, Yamanashi 409-3898 , Japan
Corresp. Author Email: nobuot@yamanashi.ac.jp
Journal : Microscopy Research and Technique (Microsc. Res. Tech.) , v70, n7, (634-639) , 2007 , United States
Publication Date: July 1, 2007 (20070701)
Coden: MRTEE
ISSN: 1059-910X **eISSN:** 1097-0029
DOI: http://dx.doi.org/10.1002/jemt.20449
Record Type: Abstract; New
Document Type: Article
Languages: English **Summary Languages:** English
No. of References: 20

The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying. Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy.

Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively. Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue. (c) 2007 Wiley-Liss, Inc.

Descriptors:
Freeze-drying; In vivo cryotechnique; Mapping; Raman microscopy; Raman spectrum

Classification Code and Description:
89 (CELL AND DEVELOPMENTAL BIOLOGY)
89.13 (METHODOLOGY)
89.13.1 (Techniques)
89.13.1.3 (Microscopy)

Record History: New; Created: July 20, 2007 (20070720) ; Delivered: June 22, 2008 (20080622)
Dialog Update Date: 20081211; 08:07:19 EST

13/9/11 (Item 1 from file: 73)
DIALOG(R)File 73: EMBASE

0071381872 **EMBASE No:** 1979114101
Analysis of iron content in individual human red blood cells by electron microprobe and scanning electron microscope

Davis D.
Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States
Corresp. Author/Affil: : Donner Lab., Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720, United States

Micron (MICRON) (United Kingdom) December 1, 1978 , 9/4 (175-190)
CODEN: MICNB **ISSN:** 0968-4328
Document Type: Journal **Record Type:** Abstract
Language: English

The iron content of single human red blood cells has been assessed using electron microprobe analysis and scanning electron microscope. Cells for microanalysis consist of a fixed-washed and freeze-dried preparation. This preparative procedure improves stability and spatial resolution of the analytic method. The reference standard employs compressed pellets of purified iron-containing human hemoglobin and human albumin, respectively. The cell preparation and reference standard remain stable for long periods of time. Differences in Fe content and its distribution among individual red cells from both normal subjects and sickle cell anaemia patients have been measured by the quantitative and semiquantitative techniques (wavelength and energy dispersive X-ray spectrometry). There are several points which can be made from this study. One concerns the estimate of iron on a cell by cell basis, the average variation can be made from this study. One concerns the estimate of iron on a cell by cell basis, the average variation among cells being slightly over 13%, ranging from 6% to 19.4% by individuals (samples) or from 11% to 14% by ethnic groups. These differences are thus closely comparable across ethnic grouping with a possibility of high level in Asians and lower level in sickle cell anaemia patients.

Drug Descriptors:
* iron
Medical Descriptors:
* erythrocyte
blood and hemopoietic system; cytology; diagnosis; methodology
CAS Registry Number: 14093-02-8, 53858-86-9, 7439-89-6 (iron)
SECTION HEADINGS:
Anatomy, Anthropology, Embryology and Histology
Hematology

0070101518 **EMBASE No:** 1974101617
Iron ATP, a by product of acid extraction of whole blood or red blood cells

Meyers N.L.; Brewer G.J.; Oelshlegel Jr F.J.
Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann Arbor, Mich. 48104, United States
Corresp. Author/Affil: : Dept. Hum. Genet. Med., Univ. Michigan Med. Sch., Ann

Arbor, Mich. 48104, United States

Biochimica et Biophysica Acta (BIOCHIM. BIOPHYS. ACTA) December 1, 1973 , 320/2 (397-405)
CODEN: BBACA **ISSN:** 0006-3002
Document Type: Journal ; Article **Record Type:** Abstract
Language: English

Trichloroacetic acid extracts of red cells often produce an iron ATP complex after ion exchange chromatography of the extract amounting to about 1/3 of the total ATP. In the present work the presence of 14-50% of iron ATP in such extracts from human and Rhesus monkey blood has been shown. Experiments designed to clarify the possible role and origin of iron ATP revealed that non acid treatment of human whole blood or red cells, as in the freeze thaw process, followed by separation on a Sephadex column did not produce an iron ATP fraction. In addition, purified hemoglobin and ATP were combined and incubated at pH 7.4. After Sephadex chromatography, there was no evidence of an iron ATP fraction. However, similar combinations of incubated hemoglobin and ATP treated with trichloroacetic acid and separated by ion exchange chromatography did produce an iron ATP fraction similar to that obtained from acid extracted blood. It appears that iron ATP in quantities found in acid extracted blood is the result of iron release from hemoglobin and the subsequent complexing of such iron with available ATP.

Drug Descriptors:
* adenosine triphosphate
unclassified drug
Medical Descriptors:
* erythrocyte
article; in vitro study; normal human; theoretical study
Drug Terms (Uncontrolled): caffeic acid rhamnoglucoside
CAS Registry Number: 15237-44-2, 56-65-5, 987-65-5 (adenosine triphosphate)
SECTION HEADINGS:
Clinical and Experimental Biochemistry
Hematology

0000571468 (THIS IS THE FULLTEXT)

Studies in the area of microscopy reported from University of Yamanashi
Life Science Weekly, July 24, 2007, p.2754

DOCUMENT TYPE: Expanded Reporting
LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 427

TEXT:

New research, "Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique"," is the subject of a report. "The wavelength of Raman-scattered light depends on the molecular composition of the substance. This is the first attempt to acquire Raman spectra of a mouse eyeball removed from a living mouse, in which the eyeball was preserved using the "in vivo cryotechnique" followed by freeze-drying," scientists writing in the journal Microscopy Research and Technique report. "Eyeballs were cryofixed using a rapid freezing cryotechnique, and then sliced in the cryostat machine. The slices were sandwiched between glass slides, freeze-dried, and analyzed with confocal Raman microscopy. Important areas including various eyeball tissue layers were selected using bright-field microscopy, and then the Raman spectra were obtained at 240 locations. Four typical patterns of Raman spectra were electronically mapped on the specimen images obtained by the bright-field microscopy. Tissue organization was confirmed by embedding the same eyeball slice used for Raman spectra into epoxy resin and the thick sections were prepared with the inverted capsule method. Each Raman spectral pattern represents a different histological layer in the eyeball which was mapped by comparing the images of toluidine blue staining and Raman mapping with different colors. In the choroid and pigment cell layer, the Raman spectrum had two peaks, corresponding to melanin. Some of the peaks of the Raman spectra obtained from the blood vessels in sclera and the photoreceptor layer were similar to those obtained from the purified hemoglobin and rhodopsin proteins, respectively," wrote N. Terada and colleagues, University of Yamanashi. The researchers concluded: "Our experimental protocol can distinguish different tissue components with Raman microscopy; therefore, this method can be very useful for examining the distribution of a biological structures and/or chemical components in rapidly frozen freeze-dried tissue." Terada and colleagues published their study in

n Microscopy Research and Technique (Raman microscopy of freeze-dried mouse eyeball-slice in conjunction with the "in vivo cryotechnique" Microscopy Research and Technique , 2007;70(7):634-9). Additional information can be obtained by contacting N. Terada, University of Yamanashi, Dept. of Anatomy, Interdisciplinary Graduate School of Medicine and Engineering, Chuo-city, Yamanashi 409-3898, Japan. The publisher of the journal Microscopy Research and Technique can be contacted at: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030, USA. Keywords: Japan, Yamanashi, Microscopy. This article was prepared by Life Science Weekly editors from staff and other reports.

DESCRIPTORS: All News; Professional News; All News; Professional News
SUBJECT HEADING: Microscopy

13/9/14 (Item 2 from file: 135)
DIALOG(R)File 135: NewsRx Weekly Reports

0000000087 (THIS IS THE FULLTEXT)

Hemolink Phase II Trials to Begin in 1996
AIDS Weekly, December 25, 1995, p.11-12

DOCUMENT TYPE: Editor's Choice
LANGUAGE: English
RECORD TYPE: FULLTEXT
AUDIENCE: Professional
WORD COUNT: 763

TEXT:

A red blood cell substitute will go into Phase II clinical trials early in 1996 and, if all goes well, could be available on the market by 1999.

The announcement was made at the 1995 International Chemical Congress of Pacific Basin Societies, held in Honolulu, Hawaii, December 17-22, 1995.

The blood substitute, Hemolink, manufactured by Hemosol, is made of chemically modified hemoglobin, says Dr. Gord Adamson, a company scientist. Hemolink is derived from screened and tested blood that is outdated because it has been stored for more than six weeks.

Hemosol takes the expired blood, separates out the red blood cells and extracts the hemoglobin. That's more complicated than it sounds. "A red cell is not just a package of clean hemoglobin," Adamson says. "It contains about 90 different proteins." The company heat-treats the hemoglobin to destroy any contaminating viruses that may have eluded the screening process conducted by collection agencies. Other remaining proteins are then removed by a novel displacement chromatographic process.

The process strips away blood-group antigens and other proteins, so Hemolink can be used by all patients regardless of blood type. And the purification steps make the likelihood of transmission of diseases such as HIV and hepatitis "virtually" nil, according to Adamson.

"The reason we say 'virtually,'" he notes, "is because scientifically it is impossible to prove total absence of a virus," but he is very confident that Hemolink would pose no threat to users in terms of blood-borne diseases. In addition, the blood from which Hemolink is derived is already approved for use; the company does not accept contaminated units.

After purification, the free hemoglobin is cross-linked with oxidized raffinose, a sugar molecule. This "improves the ability of the free hemoglobin to deliver oxygen to tissue, stabilizes each hemoglobin molecule and links together several such molecules so that

they are large enough to circulate for extended periods," Adamson says.

Human trials with Hemolink show the blood substitute circulates for a couple of days in the blood stream - compared with a month or more for transfused red cells - and is then excreted, says Adamson. But animal trials show this is long enough to counteract oxygen shortages during acute blood loss, say, in an accident or an operation. In fact, these trials showed that animals treated with Hemolink did just as well as those treated with transfusions of the animals' own blood.

Hemosol is currently working with two versions of Hemolink, one a fluid stored in a refrigerator and one frozen. Either formulation would be suitable for surgical applications. A long-term goal is to develop a freeze-dried formulation. It would be light enough to ship to remote depots - for use in disasters or military conflicts, for example - and it could be reconstituted with sterile water on-site.

Adamson believes the cost for Hemolink would be competitive, noting that there are significant administrative costs associated with the existing blood collection and distribution system. These include the storage, transport, disposal and other labor and record-keeping activities that a successful blood substitute would significantly reduce. Also, since no cross-matching would be required, these costs would be saved.

Hemolink also would avoid some of the costly problems associated with blood transfusions - such as transmission of disease (ranging from HIV or hepatitis to a bacterial infection), or mismatched blood (where the patient might have a reaction to antigens in the donor's blood that could be mild, such as a fever, or severe, resulting in death), or the delays in surgery brought about by blood shortages.

Hemosol will not rely just on Hemolink to launch itself in this market. The company is collaborating with Ronald Kluger, a chemistry professor with the University of Toronto, Ontario, Canada, to further extend cross-linking technologies for second-generation products.

Adamson says the work also is aimed at chemically modifying hemoglobin so it can serve as a carrier for drug molecules. Tissues that can accumulate and metabolize protein-drug conjugates are potential targets. An example is a solid tumor. Adamson says this would reduce many of the side-effects of anti-tumor agents.

A large-scale conversion from red cells to blood substitutes is unrealistic, particularly in the short term, Adamson says. But assuming they win approval, blood substitutes could ultimately bring in big money. Industry estimates of the potential market for blood substitutes (and newer applications where red cells can't be used) by the year 2002 are around 1.5 million units (worth US$500 million) in North America, and over three million units worldwide, Hemosol says.

DESCRIPTORS: news
SUBJECT HEADING: Industry News (Blood Substitutes)

01812276 **Supplier Number:** 53480462 (THIS IS THE FULL TEXT)
Blood relations.(Hemosol Inc's packaging for blood substitute products)

Canadian Packaging , 51 , 11 , 34(1)
Nov ,
1998
Publication Format: Magazine/Journal
ISSN: 0008-4654
Language: English
Record Type: Fulltext **Target Audience:** Trade
Word Count: 1076 **Line Count:** 00094

Text:
SPECIAL TO CANADIAN PACKAGING

If you're in the business of manufacturing a blood substitute product that ends up infused into a human body, product quality is understandably a paramount consideration.

And for Toronto-based Hemosol Inc., achieving that level of quality meant making a clear connection between product quality and the type of material used to package its rather unconventional product.

In its quest to maintain product stability and preserve product efficacy, Hemosol turned to a transparent flexible laminate that offered the promise of the highest barrier levels. Manufactured by Rollprint Packaging Products of Addison, Ill., the company's newest laminate in its ClearFoil family of films - called ClearFoil SiOX-F - turned out to be just such a material.

"Hemoglobin products are very oxygen-sensitive. We had to find a packaging material that would keep the gas permeability to a minimum," explains Dr. Dirk Alkema, vice-president of manufacturing at Hemosol.

"The ClearFoil film meets our specifications for high oxygen and moisture barrier properties, while the clarity of the material maintains our product's visibility."

The development of blood substitute products has its roots in military research into overcoming the issues of blood availability and stability in the field.

In the mid-80s, privately-owned Hemosol was formed to commercialize a blood substitute technology based on research conducted at Canada's Department of Natural Defense.

Its flagship product - Hemolink - is manufactured from highly purified human hemoglobin and is currently undergoing four Phase II trials in three countries - Canada, the U.S. and the U.K.

"The need for a blood substitute also arises from concerns about

viral contamination of the blood supply with HIV and Hepatitis, and even unknown viruses that are not currently screened for by the Red Cross or other blood collection agencies," notes Dr. Peter Wojciechowski, Hemosol's manager of process development.

"In addition, concerns of cross-matching blood types and periodic shortages of donated blood fuel the demand for alternatives to allogeneic or donated blood."

Hemosol packages Hemolink in an IV infusion bag that resembles those used for allogeneic blood. Originally, when Hemosol searched for an overpouch simply to maintain the cleanliness of the IV bag, it selected a nylon overpouch, which was fine for what at the time was produced primarily as a frozen product.

"We realized we could increase product shelf-life tremendously and simultaneously increase product storage temperatures if we improved the barrier properties of the overpouch," says special products manager Sam Teleki.

"We started analyzing the permeability of many different laminates from a variety of different manufacturers."

About a year ago, Hemosol learned of Rollprint's family of ClearFoil laminates - engineered to provide exceptionally high barrier levels in combination with good clarity qualities. While Rollprint offers many high-barrier laminates to match a wide variety of applications, Hemosol selected Rollprint's highest-barrier ClearFoil film in order to minimize gas permeability. This new, three-layer laminate uses ClearFoil SiOX-F material sandwiched between a 2.5-mm sealant layer and a 75-gauge oriented polypropylene (OPP) layer.

"We manufacture a highly purified blood product that carries oxygen," Alkema says. "To protect the efficacy of the product, we need to keep the gas permeability to a minimum."

The ClearFoil SiOX-F laminate also provides high moisture barrier that is of vital importance to Hemosol allowing water vapor permeability of only 0.02 grams per 100 square inches per day.

"Minimizing water vapor loss protects product concentration," Teleki explains. "For example, if we produce a product with a 10-per cent concentration of hemoglobin, fill 100 milliliters into an IV bag, and then we lose three milliliters of moisture during the shelf-life of the product, we've just increased the product concentration to 10.3 per cent."

Compared to the shelf-life of allogeneic blood that is limited to less than 42 days, Hemolink packed in Rollprint's ClearFoil SiOX-F overpouch achieves tremendous improvements.

"We haven't finalized our data yet, but the shelf-life of the Hemolink product looks promising," Alkema notes. "We're projecting we have at least a two-year shelf-life at four degrees Celsius and at least one-year shelf-life at room temperature."

While high temperatures challenge the stability of all blood products, it is the lower temperatures that tend to challenge flexible films.

"Flex crack resistance becomes more difficult at cold temperatures because some plastics become very brittle. If the overpouch is punctured or cracked, we lose package integrity," Teleki notes.

"The flex crack characteristics of the ClearFoil laminate are good, even at very low temperatures. We should know, one of our products is stored at minus 80 degrees Celsius and the material is still pliable."

If high-level barrier was all Hemosol was interested in, it could have been satisfied with a foil pouch, but the company also hoped to offer a package with good clarity. The clarity of the ClearFoil SiOX-F laminate allows for the visual monitoring of the product and increases product acceptance.

"Clinicians are used to seeing blood in an IV bag. They visually inspect the blood, checking the color of the product as an indication of product quality. We wanted to offer our product in a similar package so people would be comfortable using it," Wojciechowski explains. "The clarity of the ClearFoil overpouch allows the clinicians to easily see the IV bag and the blood product inside."

With as many as seven companies racing to be the first to win FDA approval for a blood substitute product, Hemosol is continuously making concerted efforts to maximize product efficacy and safety.

"One thing that sets us apart is our process. We believe we have the most highly purified human hemoglobin and a superior stabilizing process that give us a longer circulating half-life," Alkema says. "Market demand projections for a blood substitute product are estimated at three milton units per year in North America alone. We're hoping to be licensed and marketing the product by the year 2001. At that point, we would be handling much larger batch runs.

"We are a small company with a small production volume but a promising future. Rollprint's willingness to work with us to develop a new product is impressive," Alkema says. "We just asked for help finding a low gas permeable membrane and they went to work to identify the combination of laminates that would meet our needs. They're helping us to make the blood

supply safer, more economical, and easier to manage."

Special Features: illustration; 1
Company Names: Hemosol Inc.--Products
Descriptors: Blood substitutes--Packaging; Blood products--Packaging; Packaging industry --Products
Geographic Codes/Names: 1USA United States
SIC Codes: 2836 Biological products exc. diagnostic; 2670 Misc. Converted Paper Products
Event Codes/Names: 460 Use of materials & supplies
Product/Industry Names: 2833440 (Synthetic Blood); 2649910 (Sterilized Medical Packaging)
File Segment: TI File 148

13/9/16 (Item 2 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

01641618 **Supplier Number:** 18748015 (THIS IS THE FULL TEXT)
Blood substitute offers advantages. (experimental Hemolink, a red blood cell substitute from Hemosol Inc, does not possess the disadvantages of donated blood)(Brief Article)

USA Today (Magazine) , v124 , n2609 , p13(1)
Feb ,
1996
Document Type: Brief Article **Publication Format:** Magazine/Journal
ISSN: 0161-7389
Language: English
Record Type: Fulltext **Target Audience:** Consumer
Word Count: 459 **Line Count:** 00041

Text:
Blood donated for transfusions has several drawbacks: it must be used within five or six weeks, might carry viruses such as HIV, and only can be given to patients with a compatible blood type. These and other problems result in periodic blood shortages. However, a red blood cell substitute without these flaws is going into human safety/efficacy trials early in 1996 and, if all goes well, could be available on the market by 1999.

An average adult has about five quarts of blood, encompassing a complex

mixture of red and white cells, plasma, and platelets. The red cells contain the oxygen-carrying molecule hemoglobin, which lies at the heart of the blood substitute being developed by Hemosol Inc., based in Etobicoke, Ont., Canada. Called Hemolink, it is made of chemically modified hemoglobin, derived from screened and tested blood that is outdated because it has been stored for more than six weeks.

The process takes the expired blood, separates out the red blood cells, and extracts the hemoglobin. That is more complicated than it sounds. "A red cell is not just a package of clean hemoglobin," notes Gord Adamson, a Hemosol scientist. "It contains about 90 different proteins." The company heats the hemoglobin to destroy any contaminating viruses that may have eluded the screening process conducted by collection agencies. Other remaining proteins are removed by a displacement chromatographic process that strips away blood-group antigens and other proteins, so Hemolink can be used by all patients regardless of blood type.

The purification steps make the likelihood of transmission of diseases such as AIDS and hepatitis virtually nil, according to Adamson. "The reason we say `virtually' is because scientifically it is impossible to prove total absence of a virus." After purification, the free hemoglobin is cross-linked with oxidized raffinose, a sugar molecule. This improves its ability to deliver oxygen to tissue, stabilizes each hemoglobin molecule, and links together several such molecules so that they are large enough to circulate for extended periods.

Hemosol is working with two versions of Hemolink, one a fluid stored in a refrigerator and one frozen. Either formulation would be suitable for surgical applications. A long-term goal is to develop a freeze-dried formulation light enough to ship to remote depots - for use in disasters or military conflicts, for example - that could be reconstituted with sterile water on-site.

The substitute would avoid some of the costly problems associated with blood transfusions - such as transmission of disease (ranging from AIDS or hepatitis to a bacterial infection), mismatched blood (where the patient might have a reaction to antigens in the donor's blood that could be mild, such as a fever, or severe, resulting in death), or the delays in surgery brought about by blood shortages.

Special Features: illustration; photograph
Company Names: Hemosol Inc.--Product development
Descriptors: Blood substitutes--Innovations
File Segment: MI File 47

13/9/17 (Item 3 from file: 149)
DIALOG(R)File 149: TGG Health&Wellness DB(SM)

01193508 **Supplier Number:** 08093457 (THIS IS THE FULL TEXT)
Synthesis of functional human hemoglobin in transgenic mice.

Behringer, Richard R.; Ryan, Thomas M.; Reilly, Michael P.; Asakura, Toshio ; Palmiter, Richard D.; Brinster, Ralph L.; Townes, Tim M.
Science , v245 , n4921 , p971(3)
Sept 1 ,
1989
Publication Format: Magazine/Journal
ISSN: 0036-8075
Language: English
Record Type: Fulltext **Target Audience:** Academic
Word Count: 2144 **Line Count:** 00213

Text:
Synthesis of Functional Human Hemoglobin in Transgenic Mice

CORRECTLY REGULATED EXPRESSION of human [beta]-globin genes in transgenic mice is well documented [1, 2]. The human gene is expressed only in adult erythroid tissue and, in some animals with relatively high transgene copy numbers, the level of human [beta]-globin mRNA is equivalent to endogenous mouse [beta]-globin mRNA. Analysis of constructs with [beta]-globin gene fragments inserted upstream of a reporter gene demonstrate that sequences located immediately upstream, within and downstream of the gene contribute to the correct temporal and tissue specific expression [3]. Sequences located 50 kb upstream of the [beta]-globin gene also have an effect on globin gene expression [4-8]. When these sequences that contain erythroid-specific, DNase I super-hypersensitive (HS) sites are fused upstream of the human [beta]-globin gene and injected into fertilized mouse eggs, large amounts of human [beta]-globin mRNA are synthesized in virtually all transgenic mice that develop [5, 7]. These experiments

suggest that the super-hypersensitive sites define locus activation regions
that "open" a large chromosomal domain for expression specifically in
erythroid cells and dramatically enhance globin gene expression.

The human [alpha] 1-globin gene is also expressed at high levels in
erythroid tissue of transgenic mice when the injected gene is flanked by
super-hypersensitive sites from the human [beta]-globin locus [8]. Thus a
complete human hemoglobin could be synthesized in mice if human [alpha]-
and [beta]-globin gene constructs were coinjected into fertilized eggs.
Previous studies demonstrated that two of the five HS sites in the
[beta]-globin locus were sufficient for high-level expression [7, 8].
Therefore, we inserted HS I and II (a 12.9-kb Mlu I--Cla I fragment)
upstream of the human [alpha] 1- and [beta]-globin genes (Fig. 1) and
coinjected equimolar amounts of these constructs into fertilized mouse eggs
[9]. The eggs were transferred into the oviducts of pseudopregnant foster
mothers, and seven transgenic mouse lines were established from founder
animals that contained intact copies of the injected fragments. Total RNA
from ten tissues of adult progeny were then analyzed for correctly
initiated human [alpha]-, human [beta]-, mouse [alpha]-, and mouse
[beta]-globin mRNA by primer extension [10] (Fig. 2A). Human [alpha]- and
[beta]-globin transgenes were expressed only in blood and spleen, which are
both erythroid tissues in mice; detection in the lung is the result of
blood contamination [11] because both human and mouse [alpha]- and [beta]-
globin mRNA are observed in this nonerythroid tissue. Human [alpha]- and
[beta]-globin mRNA levels in blood, as measured by solution hybridization,
were 100% and 120% of endogenous mouse [beta]-globin mRNA, respectively.
Therefore, erythroid-specific, human [alpha]- and [beta]-globin gene
expression can be achieved in adult transgenic mice after coinjection of
[alpha]- and [beta]-globin constructs that contain HS I and II.

To determine whether complete human hemoglobins were formed, we
separated hemolysates [12] of the blood of animals from two different
transgenic lines by non-denaturing isoelectic focusing (IEF) (Fig. 2B). The
first lane is a mouse control and the last lane is a normal human sample.
The predominant band in each of the control is the major adult hemoglobin;
mouse [[alpha].sub.2.[beta].sub.2] or human
[[alpha].sub.2.[beta].sub.2]
respectively. In both transgenic mouse samples 5394 and 5393, bands that
run at the sample pI as human Hb A ([h[alpha].sub.2.h[beta].sub.2]) and

mouse hemoglobin ([m[alpha].sub.2.m[beta].sub.2]) are observed. In addition to human and mouse hemoglobins, two other major bands were observed in both transgenic samples. To determine the composition of these bands and to confirm the human and mouse hemoglobins, the four bands in sample 5393 were exercised from the gel and analyzed on a denaturing cellulose acetate strip [13] (Fig. 2C). Control lysates of mouse, human, and 5393 blood samples were separated in lanes on the left. Mouse [alpha]- and [beta]-globin polypeptides, as well as human [alpha]- and [beta]-globin polypeptides, were well separated on this strip. Sample 5393 contained all four polypeptides; the human [alpha]- and [beta]-globin polypeptides were 110% and 106% of the amounts of mouse [alpha]- and [beta]-globin, by densitometric analysis. The top band (band 1) of sample 5393 in Fig. 2B is composed of human [alpha]- and mouse [beta]-globin chains. The second band is mouse [alpha]- and mouse [beta]-globin and the third band is human [alpha]- and [beta]-globin as expected. The polypeptides composing band 4 in Fig. 2B are barely visible in Fig. 2C but are clearly mouse [alpha]- and human [beta]-globin. Therefore, normal amounts of human hemoglobin can be synthesized in adult mice, and multiple combinations of globin polypeptides are possible [see note [14]].

The functional properties of human, mouse, and hybrid hemoglobins synthesized by transgenic mice were assessed by determination of oxygen equilibrium curves (OEC) and by calculation of [P.sub.50] values. The [P.sub.50] is the partial pressure at which hemoglobin is half saturated with oxygen and is inversely related to hemoglobin oxygen affinity. All four hemoglobins described above were purified by preparative IEF [15] and the OEC for each was determined [16] (Fig. 3). The OEC were normal, sigmoid-shaped, and demonstrate that all four hemoglobins bind oxygen cooperatively. The [P.sub.50] of human hemoglobin synthesized by transgenic mice is 8.0 mmHg, which is identical to the [P.sub.50] of native human Hb A. Interestingly, the oxygen affinities of the two hybrid tetramers differ significantly from human and mouse hemoglobins. The [h[alpha].sub.2.m[beta].sub.2] hybrid has an extremely low [O.sub.2] affinity; the [P.sub.50] is 15.7 mmHg. In contrast, the [O.sub.2] affinity for [m[alpha].sub.2.h[beta].sub.2] is extremely high; the [P.sub.50] for this hemoglobin is 4.7 mmHg [17].

Finally, the hematological values of six transgenic progeny were determined and compared to five normal animals. Red blood cell counts and hematocrits for transgenic animals were normal and, interestingly, the

values for hemoglobin and mean corpuscular volume were in the normal range.
Consequently, the calculated values of mean corpuscular hemoglobin and mean
corpuscular hemoglobin concentration (MCHC) for transgenic animals were
normal. Thus the total hemoglobin concentration in transgenic erythrocytes
is not increased even though reticulocytes contain 100% more globin mRNA
[18]. Therefore, to maintain normal MCHC, all globin mRNAs are either
translated at reduced rates or [alpha]- and [beta]-globin polypeptides are
less stable. Another possibility is that globin synthesis ceases when the
maximum intracellular concentration of hemoglobin is attained. If the rate
of globin synthesis is normal, then a full complement of hemoglobin could
be synthesized in half the time leading to faster maturation of
reticulocytes.

In summary, the results presented demonstrate that high levels of human [alpha]- and [beta]-globin mRNA can be coexpressed in mice. The transgenes are expressed specifically in erythroid tissue and levels of human hemoglobin equivalent to mouse hemoglobin can be achieved. In addition, the human hemoglobin produced in these mice is fully functional
and the transgenic animals are phenotypically normal. These results provide
a solid foundation for the production of transgenic mice that synthesize
high levels of other human hemoglobins. We have initiated studies to
synthesize high levels of human sickle hemoglobin in transgenic mice in an
attempt to produce a mouse model of sickle cell disease. Although sickle
cell anemia was the first disease to be understood at the molecular level
[19], there is still no cure or adequate treatment. If a transgenic mouse
model can be developed, new drug therapies and even gene therapies could be
tested. Once perfected in model systems, protocols that are safe and
effective for humans could be developed.

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Palmiter, ibid. 82, 4438 (1985).
[10] Adult animals were made anemic with phenylhydrazine [20] to induce reticulocytosis, anesthetized, perfused [11], and tissues were removed. Total RNA was prepared from frozen tissue [Anal. Biochem. 162, 156
(1987] with the following modification. The final RNA pellets were resuspended in a solution containing 1.0% SDS, proteinase K (100 mg/ml), 25
mM NaCl, 1.0 mM EDTA, and 10 mM tris-HCl pH 7.5. After digestion for 3 hours at 50 [degrees]C, the samples were extracted with phenol/chloroform,
chloroform, and ethanol precipitated.
[11] Animals were perfused by cutting the right atrium and injecting
phosphate-buffered saline into the left ventricle. The lung is not perfused
in this procedure and, therefore, is contaminated with blood.
[12] Blood cells were washed twice with saline and lysed in a volume
of water equal to the cell pellet. One-fourth volume of carbon tetrachloride was mixed with the hemolystate, and cell membranes were extracted by brief vortexing and microcentrifugation. The aqueous phase was
removed and frozen at 20 [degrees]C. Samples were subsequently thawed, diluted with an equal volume of 0.05% KCN, and separated on an agarose isoelectric focusing gel (Resolve-Hb, Isolabs Inc., Akron, Ohio) according
to the manufacturer's specifications. After focusing, proteins were fixed
in the gel with 10% trichloroacetic acid for 10 min. The gel was then rinsed for 1 hour with water, dried, and hemoglobin bands were visualized
without staining.
[13] Hemoglobin bands were cut out of the agarose IEF gel and eluted
in water for 1 hour at room temperature. After dialysing against water overnight at room temperature, the samples were lyophilized and resuspended
in water. Equal volumes of sample (purified hemoglobin or whole

hemolysate), alkaline-urea buffer (6.0M urea, 15 mM boric acid, 0.5 mM EDTA, 25 mM tris-HCl, pH 8.6), and [beta]-mercaptoethanol were mixed and an aliquot was loaded onto a cellulose acetate strip (Gelman) that had been soaked overnight in alkaline-urea buffer. The samples were then electrophoresed for 1 hour at 19 V in alkaline-urea buffer. Proteins were subsequently stained with 0.5% imido black in methanol: acetic acid (45:10). The strips were destained in methanol: acetic acid (47.5:5), dried, and photographed.

[14] Although only four hemoglobin bands are observed on the IEF gel in Fig. 2B, nine hemoglobins representing all possible combinations of mouse and human [alpha]- and [beta]-globin polypeptides probably exist inside the cell. During electrophoresis oxy-hemoglobin tetramers ([[alpha].sub.2.[beta].sub.2]) dissociate into dimers ([[alpha].sub.1.[beta].sub.1]) that are separated by charge differences. Therefore, hemoglobin tetramers composed of dimers of unlike charge are not detected [21].

[15] Mouse, human, and hybrid hemoglobins synthesized by transgenic mice were separated by preparative IEF on 4.0% acrylamide gels containing 2.0% Pharmalyte pH 5 to 8. Each of the four bands was sliced from the gel, homogenized, and the hemoglobin was eluted in 0.1M potassium phosphate buffer. The isolated fractions were concerntrated with Amicon filters (YM 10).

[16] Hemoglobins were maintained in the carbon monoxide (CO) form during separation and concentration procedures to avoid auto-oxidation. Prior to functional studies the hemoglobins were converted to the oxy-state by photolysis and vacuum removal of CO. The oxygen equilibrium curve of each hemoglobin fraction was determined using a Hemox Analyzer (TCS, Southhampton, PA) in 0.1M potassium phosphate buffer, pH 7.0 at 20[degrees]C [22]. All samples were analyzed four times and the curves were drawn in continuous mode. The maximum error of measurement of the [P.sub.50] values is [+ or -] 1 mmHg [Crit. Care Med. 7, 391 (1979)].

[17] OEC of whole blood and unfractionated hemolysates from transgenic mice were also determined and compared to mouse and human controls. The curve for whole blood of 5393 transgenic progeny is virtually identical to the mouse control, while the curve for an unfractionated transgenic hemolysate is shifted to the left of the mouse hemolysate control. The left shift of the transgenic hemolysate OEC can be attributed to the presence of high-affinity hybrid and human hemoglobin species. The similarity of the whole blood OEC for transgenic and control mice may be due to adaptive responses, such as an increase in allosteric effectors of

oxygen affinity, in the transgenic mice.
[18] Quantitative solution hybridizations of blood RNA from the seven
transgenic lines indicate that mouse [alpha]- and [beta]-globin mRNA levels
(picograms of total RNA per microgram) are not decreased in mice expressing
high levels of human [alpha] and [beta]-globin mRNA.
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[23] We thank N. Martin, J. Askins, and M. Avarbock for excellent
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Captions: HS I,II alpha-globin and HS I,II beta-globin gene constructs. (chart); Expression of human alpha- and beta-globin genes in transgenic mice. (chart); Oxygen equilibrium curves of hemoglobins. (graph)

Special Features: illustration; chart; graph
Descriptors: Mice as laboratory animals--Research; Gene expression--Research; Hemoglobinopathy--Models; Genetic transformation--Research; Hemoglobin-- Research

File Segment: MI File 47

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13/9/18 (Item 1 from file: 162)
DIALOG(R)File 162: Global Health

0004754137 **CAB Accession Number:** 20002007317
KEMRI Hep-cell II hepatitis B surface antigen screening kit.

Okoth, F. A.; Kaiguri, P. M.; Mathenge, E.; Tuei, J.; Muchiri, S.; Owino, N.; Kamau, G.; Kulundu, J.; Njuguna, A.; Tukei, P. M.; Yano, M.; Naruse, T.
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A study was conducted at the Centre for Virus Research, Kenya Medical Research Institute (KEMRI) in Nairobi to produce a hepatitis B surface antigen (HBsAg) kit locally to screen donated and patient blood samples in Kenya. Purified HBsAg from plasma of carriers obtained from national Public Health Laboratories Services was used to immunize guineapigs to produce anti-HB antibody. The anti-Hbs was then used to sensitize sheep rbc. The final product was freeze dried (lyophilized) and its sensitivity and specificity was compared with other commercial kits. The sensitivity and specificity of KEMRI Hep-cell II was 98% and 99%, respectively. The kit was stable and potent for one year whether kept at 4 or 37(deg)C or at room temperature. It is concluded that KEMRI Hep-cell II can be successfully produced locally, and that its sensitivity and specificity is comparable to other commercial kits. The kit requires only a simple apparatus to carry out the test hence it can be used anywhere in Kenya. It is also cheap and affordable. 4 ref.

Descriptors: antigens; detection; diagnosis; diagnostic techniques; hepatitis B; human diseases; passive haemagglutination; screening
Identifiers: antigenicity; efficacy; immunogens; passive hemagglutination; screening tests
Organism Descriptors: hepatitis B virus; man
Geographic Names: Kenya
Broader Terms: Hepadnaviridae; DNA Reverse Transcribing Viruses; viruses; Homo; Hominidae; Primates; mammals; vertebrates; Chordata; animals; eukaryotes; East Africa; Africa South of Sahara; Africa; Developing Countries; ACP Countries; Commonwealth of Nations; Anglophone Africa
CABICodes: Prion, Viral, Bacterial and Fungal Pathogens of Humans, (New March

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Elevated Fetal Hemoglobin Levels in Sudden Infant Death Syndrome (Original Article)

Giulian, Gary G., B.A.; Gilbert, Enid F.; Moss, Richard L., Ph.D.
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Abstract
The cause of sudden infant death syndrome (SIDS) is unknown, although deficits in cardiopulmonary function and central respiratory control have been suggested as possible mechanisms of the disorder. In this study, we tested the hypothesis that SIDS is associated with a delay in the maturation of hematopoiesis. Prolonged elevation in the levels of fetal hemoglobin (hemoglobin F) in infants with SIDS could denote a compromised delivery of oxygen to sensitive tissue sites. Normally, hemoglobin F (alpha(sub 2)gamma(sub 2)) is largely replaced by adult hemoglobin, hemoglobin A (alpha(sub 2)beta(sub 2)), during the first six months after birth.
Using an isoelectric-focusing procedure for measuring stable hemoglobin subunits, we quantitated the levels of hemoglobin F in blood samples from 59 patients with SIDS and 40 controls (32 living and 8 dead) matched for postconceptional age. The level of hemoglobin F in the population with SIDS was significantly higher than that in the controls in the age range tested (39 to 75 weeks); the mean (+/- SEM) proportion of hemoglobin F was 63.2 +/- 3.6 percent in the group with SIDS, as compared with 48.1 +/- 5.0 percent in the controls (P<0.025). The difference in hemoglobin F levels was most pronounced 50 weeks after conception: the proportion of hemoglobin F in the 37 patients with SIDS with a postconceptional age of more than 50 weeks was 47.4 +/- 3.6 percent, as compared with 18.8 +/- 3.1 percent in the 19 controls of that age (P<0.0005).
We conclude that hemoglobin F is a useful postmortem marker for the population with SIDS that we studied and that it may have value as a prospective marker for some infants at risk for SIDS. (N Engl J Med 1987; 316:1122-6).

Text:

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SUDDEN infant death syndrome (SIDS) is responsible for approximately 2 deaths per 1000 live births in the United States, resulting in 7500 to 10,000 deaths annually. One of the most striking features of the syndrome is its age-related pattern; the incidence of SIDS peaks at two to four months after delivery, and it is rare after nine months. Research into specific mechanisms frequently suggests an association between SIDS and cardiopulmonary deficiencies, defective central respiratory control, or both (Ref. 1-4). This study was undertaken to determine whether levels of fetal hemoglobin (hemoglobin F) are elevated in patients with SIDS as compared with the levels in age-matched controls. Elevated levels of hemoglobin F at birth have previously been linked to chronic maternal anoxia (heart failure, severe bronchial asthma, and severe anemia), (Ref. 5) intrauterine growth retardation, (Ref. 6) placental insufficiency, (Ref. 7) prematurity, (Ref. 8) and maternal diabetes (Ref. 9). By eliminating (at autopsy) known clinical conditions (Ref. 10,11) associated with sustained elevations in hemoglobin F apparent in older persons (i.e., >1 month), such as sickle cell disease, hereditary persistence of fetal hemoglobin, thalassemia, hypoplastic anemia, leukemia, and trisomy 13, we found that hemoglobin F was substantially increased in the majority of patients with SIDS. Our finding was most clearly demonstrated in patients beyond 50 weeks of postconceptional age, in whom the elevation of hemoglobin F levels relative to the control values was the most pronounced.

Methods

Sample Population and Standards

Blood samples were collected at autopsies in Wisconsin and Minnesota during a five-year period (1981-1986). In all cases of death from SIDS or other known causes, complete autopsies were performed by pediatric pathologists at three centers -- the Marshfield Clinic, Marshfield, Wis. (n = 9), Minneapolis Children's Medical Center (n = 16), and the University of Wisconsin Hospital and Clinics, Madison (n = 42). Control samples were collected from normal living infants at Madison General Hospital (n = 32). All samples were collected and all tests were run under a protocol reviewed and approved by the University of Wisconsin-Madison Human Subjects Committee. We are reporting results from 59 patients with SIDS and 40 controls of comparable ages, including normal living infants (term and preterm) and 8 autopsy controls in which the cause of death was known. The autopsy findings in the controls included bronchopneumonia (n = 3), trauma (n = 3), acute aspiration pneumonia (n = 1), and the Budd-Chiari syndrome (n = 1). We also tested approximately 70 cord-blood samples (Lancaster Hospital, Lancaster, Wis., and Madison General Hospital) with regard to normal adult hemoglobin, purified globins, and commercial standards (Isolab, Akron, Ohio, and Gelman Scientific, Ann Arbor, Mich.).

Determination of Hemoglobin F at Autopsy

Whole blood (1 to 3 ml) was collected at autopsy through a heart puncture and was stored at 4 degreesC in EDTA-containing sterile vacuum tubes. Control samples (25 to 100 microliter) from living infants were collected by venous puncture and loaded into 500-microliter microfuge tubes containing 0.2 mg of Na(sub 2)EDTA in 20-microliter sterile deionized water and stored at 4 degreesC. The globin analysis was successfully used on whole blood, hemolysates, frozen blood, dried blood, and lyophilized standards. The total hemoglobin concentration was determined spectrophotometrically at 540 nm after conversion of hemolysate samples to cyanmethemoglobin (Data Medical Associates, Arlington, Tex.).

The percentage of hemoglobin F (relative to hemoglobin A) was determined by hemoglobin-subunit analysis with use of a high-voltage vertical-slab isoelectric focusing procedure (Ref. 12). Samples were mixed with a sample buffer that contained 8 M urea, 15 percent (vol/vol) glycerol, 5 percent (wt/vol) sorbitol, 2 percent (vol/vol) Triton X-100, an ampholyte concentration described previously, (Ref. 12) and 15 mM dithiothreitol. The liquid blood samples (3 microliter) were diluted to 1:10 with sample buffer and then incubated at 37 degreesC for 15 minutes, after which 1 to 3 microliter was loaded onto the acidic end of the 5.5 percent (wt/vol) polyacrylamide gel prepared with 8 M urea, 15 percent (vol/vol) glycerol, 5 percent (wt/vol) sorbitol, 1.5 percent (wt/vol) ampholyte (pH 6 to 8), 0.75 percent (wt/vol) ampholyte (pH 4 to 6), 0.75 percent (wt/vol) ampholyte (pH 5 to 7), and 0.30 percent (wt/vol) ampholyte (pH 3.5 to 10). The gels were run on an SE600 electrophoresis cell (Hoefer Scientific Instruments, San Francisco). After focusing, the gel was fixed and stained with Coomassie R-250, dried between layers of cellophane and Mylar, (Ref. 13) and scanned with a BioMed 504XL scanner (BioMed Instruments, Fullerton, Calif.). The areas under the peaks were digitally integrated to determine the relative amounts of each globin chain present. The percentage of hemoglobin F was determined by calculating the ratio of the sum of the two gamma peaks ((sup A)gamma and (sup G)gamma) over the sum of the gamma and beta peaks. Since the alpha-globin chain normally constitutes a fixed fraction of total hemoglobin at all ages, this was not included in the calculation. Dilution studies (data not shown) demonstrated a linear Coomassie staining range of approximately 0.1 to 2.5 microgram of protein for both the gamma and beta chains.

Analysis of Data

Eighteen samples were run simultaneously on the same gel, and the stained gels were analyzed for hemoglobin F content by persons who did not know the age of the infant or the cause of death (if any). Only after the hemoglobin F was measured was the sample matched with the age and outcome. The hemoglobin F values in the patients with SIDS and the age-matched controls were compared with use of Student's unpaired two-tailed t-test.

Results

Figure 1 demonstrates the accuracy of the hemoglobin F determination by means of hemoglobin-subunit analysis. Known relative amounts of hemoglobin F and hemoglobin A were compared for their relative proportions of gamma- and beta-globin chains as measured with the isoelectric-focusing protocol. Each of the points in Figure 1 represents the mean value from analyses of three separate gels, and the data showed good linearity ($r = 0.9917$) between the proportion of gamma-globin chain and the total hemoglobin F between 0 and 97.5 percent. The use of subunit analysis of denatured samples eliminated

the problems associated with heterogeneity in the charge of the heme ring in native hemoglobin tetramers. *Figure 1. Determination of Levels of Hemoglobin F (HbF) with Hemoglobin-Subunit Analysis *. **FIGURE OMITTED**
The results of an analysis of a representative gel are shown in Figure 2. Lane A contains a hemoglobin A and hemoglobin S standard with both the beta and beta (sup s) (sickle) isoforms, whereas B and C contain mixed hemoglobin F and hemoglobin A standards. The standards served as internal controls, with Lane B containing a high proportion of hemoglobin F (85 percent) and Lane C a low proportion (10 percent). Lanes 1 to 4 demonstrate the globin profiles of living controls matched for the postconceptional ages of 51 and 63 weeks (Lanes 1 and 3) with infants with SIDS (Lanes 2 and 4). The hemoglobin F levels were substantially higher in the blood from the patients with SIDS than in the blood from the controls at both 51 and 63 weeks of postconceptional age (Fig. 3). The (sup G)gamma/(sup A)gamma ratios were calculated from the scans shown in Figure 3, as follows: Lane 1, 2.2; Lane 2, 2.5; Lane 3, 0.7; and Lane 4, 1.8. Previous studies have shown that the ratio is normally 3:1 at birth and approximately 2:3 at six months of age (Ref. 14). The control samples (1 and 3 in Fig. 3) had normal (sup G)gamma/(sup A)gamma ratios for their respective ages; however, although the patients with SIDS (2 and 4) had normal ratios for the percentage of hemoglobin F present, these ratios were elevated for their postconceptional ages. *Figure 2. Electrophoretic Separation of Hemoglobin Subunits. An isoelectric-focusing gel of blood samples was loaded from the acidic side to a total of 0.5 to 2.5 microgram of globin per band. Lanes A to C contained hemoglobin standards hemoglobins A and S (AS) and hemoglobins A and F (AF). Note that although our study population was predominantly white (Table 1), the gel-analysis procedure used in this study can resolve hemoglobin F in the presence of beta (sup s). Lanes 1 to 4 contain samples from age-matched infants with SIDS and controls *. **FIGURE OMITTED** *Table 1. Characteristics of the Study Population *. **TABLE OMITTED** *Figure 3. Densitometric Scans of Globin Profile. Densitometric scans of Lanes 1 to 4 of the gel in Figure 2 are shown. The values in each panel represent the percentage of fetal hemoglobin in the corresponding blood sample *. **FIGURE OMITTED**
The results of these analyses are summarized in Figure 4, in which the percentage of hemoglobin F in the SIDS and control groups is plotted against increasing postconceptional age. Each point represents the result from an individual blood sample and is the mean of three completely separate hemoglobin F determinations (all within a 10 percent range). All samples (in both control and SIDS groups) were from infants born at least two weeks before the sample was taken; 10 infants in the control group had been born 4 to 14 weeks prematurely (Table 1). The mean (+/- 2 SD) value for the normal decline in hemoglobin F with increasing age (Fig. 4) was derived from 432 different determinations of the percentage of hemoglobin F with use of alkali denaturation, (Ref. 59) Fe labeling, and globin analysis (Ref. 15-18). We assumed a term delivery to be one that occurred at least 39 weeks after conception. *Table 1. Characteristics of the Study Population *. **TABLE OMITTED** *Figure 4. Percentage of Hemoglobin F, According to Postconceptional Age in Samples from Patients with SIDS and Controls. The solid line denotes the calculated mean value for the normal decline in hemoglobin F with increasing age, and the broken lines +/- 2 SD. Autopsy data indicated by x are from forensic cases involving homicide *. **FIGURE OMITTED**

The data on the infants with SIDS and the controls are summarized in Table 2 according to age group (less than 50 weeks -- below the midpoint of the normal steep decline in hemoglobin F Fig. 4] -- and more than 50 weeks) and in the total population (39 to 75 weeks). The hemoglobin F levels in each of the populations with SIDS were significantly elevated as compared with those in our controls and the published normal ranges, particularly those after 50 weeks of postconceptional age. *Table 2. Levels of Hemoglobin F in Subjects in Three Postconceptional Age Groups *. **TABLE OMITTED** *Figure 4. Percentage of Hemoglobin F, According to Postconceptional Age in Samples from Patients with SIDS and Controls. The solid line denotes the calculated mean value for the normal decline in hemoglobin F with increasing age, and the broken lines +/- 2 SD. Autopsy data indicated by x are from forensic cases involving homicide *. **FIGURE OMITTED**

Discussion

Investigations of possible mechanisms for SIDS have failed to provide a single hypothesis that is consistent with the diverse findings at autopsy. Steinschneider (Ref. 19) proposed that hypoventilation is a possible risk factor for SIDS, and Naeye (Ref. 20,21) subsequently found evidence of chronic hypoxemia at autopsy. Of the seven tissue markers that have been widely studied in connection with SIDS, at least three appear to have a strong association with the syndrome (Ref. 3): an increase in periadrenal brown fat, hematopoiesis in the liver, and brain-stem astrogliosis. Even these findings are somewhat controversial, (Ref. 2,22) partly because of the subjectivity involved in identifying pathological indexes and postmortem changes in tissue samples and in the selection of appropriate controls. Epidemiologic studies (Ref. 23-26) of SIDS suggest an association with low birth weight, prematurity, retarded growth development, and maternal smoking.

Although the underlying mechanisms for our findings are not known, the population of patients with SIDS that we studied had marked elevations in hemoglobin F. The reason for the abnormal persistence of hemoglobin F is uncertain, but it may be explained on the basis of a delay in the replacement of hemoglobin F by hemoglobin A. Naeye's evidence (Ref. 20) for residual liver hematopoiesis in patients with SIDS may indeed be indicative of delayed hematopoietic development, although the switch from hemoglobin F to hemoglobin A normally occurs independently of the site of hematopoiesis (Ref. 14,27). Given that the half-life of circulating fetal erythrocytes is approximately 70 days, (Ref. 27) the observed elevation in hemoglobin F in the blood of patients with SIDS would appear to be part of a process that occurs over several weeks rather than hours or minutes. This is consistent with the suggestion that chronic conditions may underlie SIDS, (Ref. 28) but it certainly does not exclude the possibility that the final event is acute obstructive hypoxia (Ref. 29-31).

Our populations were matched for postconceptional age, since the normal decline in hemoglobin F is based on the total developmental age. The majority of our patients with SIDS were delivered at or near term (Table 1); thus, consideration of gestational age would not have significantly altered the distribution of the data. Only three of our control samples were from infants who died as a result of trauma, but all the control values for hemoglobin F were within the established normal range (+/- 2 SD) when postconceptional age was taken into account. Neither our patients with SIDS nor our controls had any known hematologic disorders. Indeed, conditions that may result in

abnormally elevated levels of hemoglobin F after approximately 50 weeks, such as thalassemias, sickle cell disease, aplastic anemia, hereditary persistence of fetal hemoglobin, and leukemia, (Ref. 11) do not appear to be associated with SIDS. *Table 1. Characteristics of the Study Population *. **TABLE OMITTED**

The peak incidence of SIDS occurs among infants two to four months old -- an age at which total hemoglobin levels are normally minimal because of infant anemia (Ref. 14,27). Brown et al. (Ref. 32) have concluded that elevated hemoglobin F levels in preterm infants are of concern only under stressful conditions. Thus, an elevated hemoglobin F level and the coincident normal anemia could be benign unless there is an acute episode during which the combination of these conditions would limit oxygen tension. Consistent with this idea, the period during which the hemoglobin concentration is minimal is well correlated in time with the peak incidence of SIDS (Fig. 5), (Ref. 33) with preterm infants (who are at higher risk for SIDS) having a lower total hemoglobin level two to four months after delivery (Ref. 27). *Figure 5. Mean Total Hemoglobin (Hb) Level and the Occurrence of SIDS, According to Post-Delivery Age. The normal period of infant anemia occurs simultaneously with the peak incidence of SIDS. Preterm infants with a higher proportion of hemoglobin F also tend to have a more severe anemia after delivery, and as a group, they are at higher risk for SIDS. Total hemoglobin concentration can be measured only in living infants. Data were derived from Naeye (Ref. 33) and Dallman (Ref. 27) *. **FIGURE OMITTED**

An earlier brief report (Ref. 34) indicated that there was no difference in hemoglobin F levels between subjects with SIDS and controls. Since a full report has not yet been published, we are unable to assess possible reasons for the apparent discrepancy with our results. However, it is important to note that many commonly used methods of determining hemoglobin F content in fresh blood do not appear to be appropriate for autopsy samples. Early in the present study, both the alkali-denaturation method and native hemoglobin separation procedures were abandoned because of poor reproducibility due to the variable hemolysis of whole blood samples and oxidation of the heme ring. Furthermore, the alkali-denaturation method is also not recommended on any test material containing more than 40 percent hemoglobin F (Ref. 35) without previous dilution with hemoglobin A, (Ref. 17) since the assessment will otherwise appear to underestimate the hemoglobin F content (Ref. 18,35).

In summary, a randomly selected population of infants with SIDS diagnosed by means of a complete autopsy was found to have elevated levels of hemoglobin F relative to those in age-matched controls. Our interpretation of this finding is that infants with SIDS are characterized by a marked delay in the switch from hemoglobin F to hemoglobin A -- a phenomenon that may reflect an underlying chronic condition. Although the conditions that predispose to a SIDS episode remain elusive, the finding of an elevation in hemoglobin F level may be useful as a diagnostic postmortem indicator for SIDS and may have value as a prospective marker for some infants at risk for SIDS, especially those beyond 50 weeks of postconceptional age.

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? **s ((red blood cells) or (red blood cell) or (RBC))(n100)(freeze or frozen or freez? or (-80))**

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30725  RED BLOOD CELLS
51992  RED BLOOD CELL
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        107703  RBC
        257152  FREEZE
        445425  FROZEN
        524974  FREEZ?
             0  -80
S14        1966  ((RED BLOOD CELLS) OR (RED BLOOD CELL) OR
                 (RBC))(N100)(FREEZE OR FROZEN OR FREEZ? OR (-80))
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? **s s14(n50)(lys?)**

Processing

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       1929442  LYS?
S15         52  S14(N50)(LYS?)
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Please enter a command or be logged off in 5 minutes

? **logoff**

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            $2.16  9 Type(s) in Format  9
         $5.52  23 Types
$10.96  Estimated cost File155
         $6.40    1.035 DialUnits File5
            $9.76  4 Type(s) in Format  3
         $9.76  4 Types
$16.16  Estimated cost File5
         $1.28    0.198 DialUnits File24
            $5.40  2 Type(s) in Format  3
         $5.40  2 Types
 $6.68  Estimated cost File24
         $0.44    0.068 DialUnits File28
 $0.44  Estimated cost File28
        $17.04    0.598 DialUnits File34
            $8.28  1 Type(s) in Format  3
         $8.28  1 Types
$25.32  Estimated cost File34
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 $0.41  Estimated cost File35
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 $0.49  Estimated cost File40
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            $7.67  2 Types
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    $10.40  INTERNET
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   $204.41  Estimated total session cost  10.654 DialUnits


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